Synthesis of α-Vinylboron Compounds via the Palladium-Catalyzed Regioselective Mizoroki-Heck Reaction

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Abstract

Developing more efficient and robust reaction methodologies is one of the paramount objectives for synthetic chemists. The creation of novel reactions provides chemists with access to a diverse range of molecular structures, which also advances the development of related scientific fields. A notable example is the metal-catalyzed cross-coupling reaction to form carbon–carbon and carbon–heteroatom bonds, which considered as one of the most significant advancements from the last half century of synthetic organic chemistry, has emerged as the most extensively employed reaction class in medicinal chemistry to synthesize pharmaceutical compounds. In the Newman lab, the research interests are based on methodology development with transition-metal catalysts and design of ligands. Chapter 1 gives an overview of cross-couplings, Mizoroki-Heck reactions, and the development of 1,5-diaza-3,7-diphosphacyclooctane (P_2N_2) ligands in metal-catalyzed organic transformations. Chapter 2 describes our efforts in developing of highly regioselective Mizoroki-Heck reactions for the synthesis of α-vinylboron compounds by employing Pd/P_2N_2 catalyst system. This reaction aims to offer a rapid and reliable method for obtaining α-vinylboron compounds, recognized as valuable building blocks in organic synthesis.

Acknowledgements

First of all, I would like to thank Professor Stephen Newman for allowing me to conduct research in his lab and always being supportive to me. I would not forget the countless chats and discussion we had in your office whenever I have any questions (whether it is related to chemistry or not). The constant interaction with you meant a lot to me and definitely helped me grow into a better chemist and a better person.

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I would also like to thank my parents, Wen Chen (陈文) and Ling Du (杜玲), I would never think I can study in a subject that I enjoy and now pursing a career in it without your supports all along my life.

Last but not least, I would like to give a special mention to my partner Kexin Tian (田可欣), who changed my life completely. Without you, I would probably still be unclear about where and how to spend my life after my degrees, and I would probably take a much longer time or even never be able to find my way as a researcher to explore the boundary of science. I really appreciate the many amazing years and wonderful time we had so far since we met, and I give all the credits to you. Our future is coming up and I am confident that we both are going to enjoy it!

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Abbreviations

9-BBN	9-borabicyclo(3.3.1)nonane
Å	Angstroms
Ac	acetyl
Ar	generic aromatic group
ArCF3	4-(trifluoromethyl)phenyl group
ArOMe	4-methoxyphenyl group
Bn	benzyl
Boc	tert-butyloxycarbonyl
bipy	2,2′-bipyridine

Bu	butyl
Cy	cyclohexyl
Cp	cyclopentadienyl
cod	1,5-cyclooctadiene
dan	1,8-diaminonaphthalene
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dcype	1,2-bis(dicyclohexylphosphino)ethane
DFT	density-functional theory
DIPEA	N,N-diisopropylethylamine; also called Hunig's base
DIPPE	1,2-bis(diisopropylphosphino)ethane
DMA	N,N-dimethylacetamide
DMF	dimethylformamide
dnpf	1,10-bis[di-(1-naphthyl)phosphino]-ferrocene
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
EI	electron-ionization

equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate
FID	flame ionization detector
GC	gas chromatography
Hex	hexyl
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	coupling constant
L	generic ligand
M	generic metal, or molar
Me	methyl group
MeCN	acetonitrile
MeOH	methanol
MHz	megaHertz
MIDA	N-methyliminodiacetic acid
MS	mass spectrometry
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance spectroscopy

OAc	acetate
OMs	mesylate
OTf	triflate or trifluoromethanesulfonate
P_2N_2	1,5-diaza-3,7-diphosphacyclooctane
Ph	phenyl
PhMe	toluene
PhF	fluorobenzene
pin	pinacol group
R	generic carbon group
rac	racemic
^{t}Bu	tert-butyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetate
THF	tetrahydrofuran
TLC	thin-layer chromatography
TM	transition-metal
TMP	2,2,6,6-tetramethypiperidine
X	generic halogen/heteroatom

Statement of Contributions

The initial discovery of the work in Chapter 2 was done by a senior student in the lab Eric Isbrandt (PhD). The project was then taken over by me and carried out the reactions discussed in this thesis. While I conducted most of the experiments for this project, we regularly discussed result and the project's direction. Compound **7** was synthesized and characterized by Eric. P_2N_2 ligands employed in this project were mainly synthesized by Eric and some were by previous lab members. Unless otherwise noted, all of the other experiments and characterizations were performed and obtained by me.

This research project has been presented in the following conference:

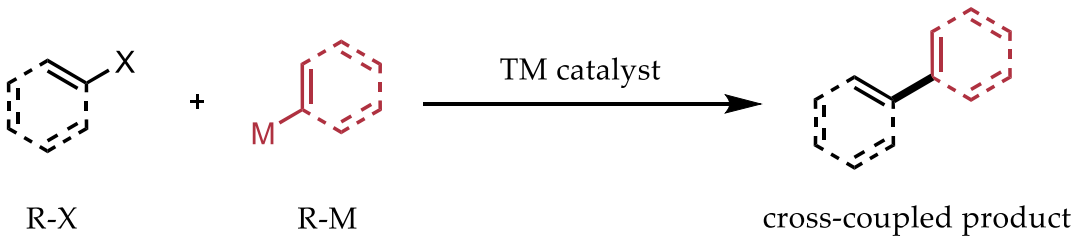
1. Chen, Z., Isbrandt, E. S., Newman, S. G.; Controlling the Regioselectivity in Pd-catalyzed Intermolecular Mizoroki-Heck Reaction: Towards the Synthesis of α-Vinylboronates; oral presentation; at Ottawa-Carleton Chemistry Institute Day Annual Graduate Research Meeting (OCCI Day 2023); May 2023.
2. Chen, Z., Isbrandt, E. S., Newman, S. G.; Controlling the Regioselectivity in Pd-catalyzed Intermolecular Mizoroki-Heck Reaction: Towards the Synthesis of α-Vinylboronates; oral presentation; at Canadian Chemistry Conference and Exhibition (CSC2023); June 2023.
3. Chen, Z., Isbrandt, E. S., Newman, S. G.; Synthesis of α-vinylboronates through Pd-catalyzed Regioselective Mizoroki-Heck Reaction; poster presentation; at 48th National Organic Chemistry Symposium (NOS2023); July 2023.

Chapter 1 Transition-Metal Catalysis and Mizoroki-Heck Reaction

1.1 Transition-metal catalyzed cross-coupling reactions

Transition metals (TM) are widely used tools in synthetic organic chemistry owing to their ability to interact with organic molecules and drive organic transformations. Since their discovery in the 1970s, transition metal-catalyzed substitution reactions, broadly known as cross-coupling reactions, have developed into one of the most used reactions in the synthesis of pharmaceuticals, natural products, and conjugated organic materials.[1] The traditional cross-coupling reaction usually connects two sp^2 carbon-based building blocks and forms a new carbon—carbon bond. A generic reaction scheme of cross-coupling reactions is shown in Scheme 1.

Scheme 1. Transition-metal catalyzed cross-coupling reactions

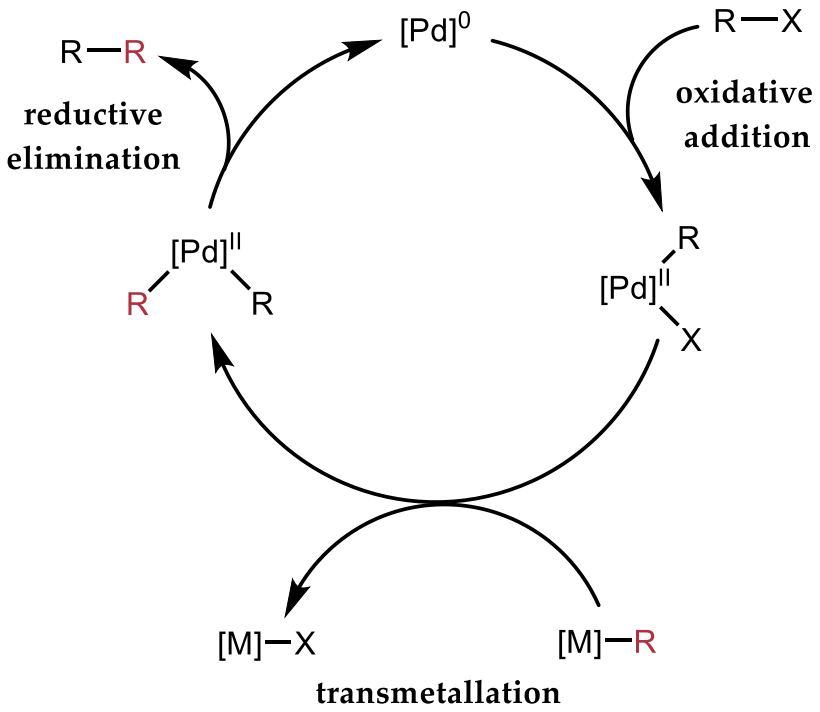


The two coupling partners, denoted as R—X and R—M, are sometimes referred to as the electrophile and nucleophile in the cross-coupling reactions, respectively. The X groups are usually halides (I, Br, Cl) or pseudohalides (triflate, tosylate, etc.) that dictate the electrophilic site that interacts with the transition metal. The nucleophile R-M is usually an organometallic reagent such as organomagnesium, organozinc, or organoboron reagents. In section 1.1.2, a range of cross-coupling reagents and reactions with be discussed in detail.

1.1.1 Mechanism of cross-coupling reactions

The mechanism of a general cross-coupling reaction usually involves three elementary steps, except for the Mizoroki-Heck reaction which will be discussed in section 1.2. A generic mechanism of a palladium-catalyzed cross-coupling reaction is shown in Scheme 2 highlighting the three stages: oxidative addition, transmetallation, and reductive elimination. The notation of [Pd] indicates that the Pd center is bound to unspecified ligands. Ligands (L) are molecules that can modify the steric and electronic profiles of the transition-metal catalyst, often by acting as Lewis bases upon the metal center. They usually play an important role in enabling reactivity and controlling selectivity in many of the metal-catalyzed reactions.

Scheme 2. Generic mechanism of palladium-catalyzed cross-coupling reaction



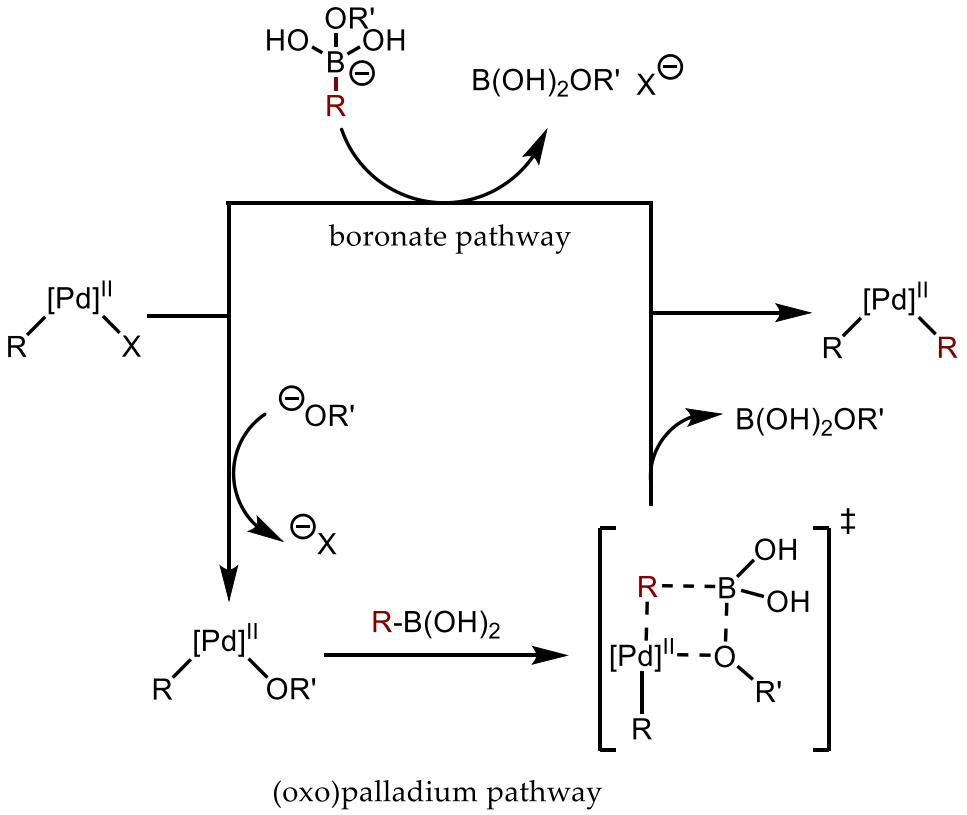
Starting from the Pd(0) complex, oxidative addition is the first step and occurs with the electrophile R—X adding across the Pd center to form an R—Pd^{II}—X complex.

With a Pd catalyst, this step is usually a two-electron transfer process and increases the oxidation state of Pd by 2. Since this step takes electrons away from the metal center, electron-rich metal centers are often favored. A metal with lower electronegativity is considered to be more electron-rich, accounting for Ni(0) undergoes oxidative addition more readily than Pd(0) since nickel is a less electronegative metal. A low-valent metal center can also undergo oxidative addition more easily than a high-valent metal center. As an example, Pd(0)→Pd(II) oxidative addition is very common with electrophiles such as aryl halide; however, Pd(II)→Pd(IV) oxidative addition is much more challenging and requires strongly electrophilic reagents to achieve.[2] The choice of proper ligands can lead to more facile oxidative addition as ligands are capable of tuning the electronic and steric properties of the metal center. It is believed that electron-donating and sterically demanding ligands can facilitate oxidative addition. This type of ligand can result in the transition-metal center becoming electron-rich and existing as a less hindered monoligated form, which makes it easier for the substrate to bind.[3] Another factor that affects the reactivity of the oxidative addition is the nature of the electrophiles. The bond strength of the C—X bond is usually associated with the reactivity. The stronger the C—X bond, the harder it is to break during oxidative addition. As a result, the relative rates for oxidative addition of aryl halides are usually observed as follows: Ar—I > Ar—Br > Ar—Cl. Aryl triflate (Ar—OTf), which is used extensively in the project discussed in Chapter 2, is commonly believed to have similar reactivity as aryl bromide.[4] However, even though the bond strength can give a prediction on the reactivity, many exceptions to this trend have been reported and the actual reactivity is usually determined by the nature of the catalyst/ligand and reaction conditions.[5–7] Besides the C—X bond, the electronic nature of the aryl ring also influences the reactivity and the rate of oxidative addition. Aryl halides bearing electron-withdrawing groups react faster than aryl halides bearing electron-donating groups. For instance, 4-bromobenzonitrile can undergo

oxidative addition faster than 4-bromoanisole.[1]

The second step in the cross-coupling reaction is called the transmetallation, which involves the replacement of the halide/pseudohalide with an organic group from the nucleophilic reagent including but not limited to organomagnesium, organozinc, and organoboron compounds. The oxidation state of the central metal remains the same during this ligand exchange process. The mechanism of transmetallation is less studied in-depth and likely to be more complicated compared to other elementary steps. For strongly polarized transmetallating reagents such as organomagnesiums, transmetallation can be considered as a concerted mechanism to generate the R—Pd(II)—R species and metal salts. For less polarized reagents such as organoborons and organosilicons, the transmetallation is believed to be stepwise with multiple pathways suggested. Taking the transmetallation with organoboron compounds as an example, two pathways have been suggested as shown in Scheme 3.[8] A base such as alkoxide is required to facilitate this transmetallation. Path A suggests that the alkoxide is coordinated to the empty orbital on the boron producing boronate anion, which makes the organoboron compound more polarized and nucleophilic to facilitate the transmetallation. An alternative pathway of transmetallating organoboron compounds involves the formation of a palladium alkoxide complex. Such species can undergo transmetallation with an equivalent of the organoboron species without the need for a base. Either pathway in the transmetallation of organoboron species could be dominant depending on the nature of the organoboron reagent.[9,10]

Scheme 3. Suggested pathways for transmetallation of organoboron species



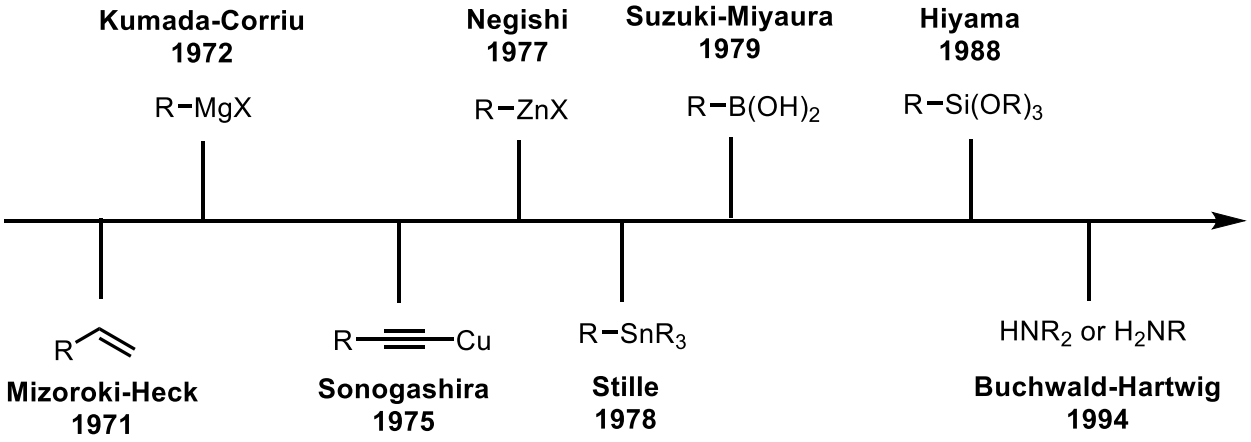
Reductive elimination is the last step and the product-forming step of a cross-coupling reaction. The carbon—carbon bond is formed and the Pd(II) intermediate is reduced back to Pd(0) to complete the cycle. This step is the reverse of oxidative addition, thus unlike in oxidative addition, an electron-deficient metal center would favor the reductive elimination. For group 10 metals, this step is rapid in the formation of $C(sp^2)$—$C(sp^2)$ bonds but becomes slower in the formation of $C(sp^3)$—$C(sp^3)$ bonds. In addition, the reductive elimination requires the two target carbons *cis* to each other instead of *trans* over the metal. Regarding this, bidentate phosphine ligands are often used to force the *cis* configuration and facilitate the reductive elimination.[11]

1.1.2 Development of cross-coupling reactions

The cross-coupling reactions quickly expanded in the late 20th century due to the

development of various nucleophilic coupling partners. Here, some of the examples are listed chronologically (Scheme 4). In 1971 and 1972, Mizoroki and Heck independently discovered the arylation of olefins with aryl halides in the presence of a palladium catalyst.[12,13] Later, Kumada and Corriu both reported a cross-coupling reaction with aryl halides and Grignard reagents (RMgX) using a nickel catalyst.[14,15] While Grignard reagents are readily available, this reaction was not widely used due to the low functional group tolerance. Since then, many other organometallic reagents have been used to expand the scope of cross-coupling reactions. In 1975, Sonogashira developed the mild alkynylation of aryl halides using copper acetylide nucleophiles generated in situ in the reaction with palladium catalyst.[16] Two years later, Negishi reported using organozinc reagents as nucleophiles to cross-couple with aryl halides.[17] Organotin compounds are later found to be a great candidate for the coupling of acyl and aryl halides based on the studies by Stille and others.[18–20] Since then, the development of mild and easy-handle reagents gained more interest in cross-couplings. Suzuki and Miyaura first discovered and continued to develop the use of organoboron reagents as the cross-coupling nucleophiles in palladium-catalyzed conditions with the addition of bases.[21] This reaction has now become the most widely used cross-coupling reaction in organic synthesis due to the less toxic and easily handled organoboron reagents and broad reaction scope. Several organoboron compounds have been employed in Suzuki-Miyaura coupling, including boronic acids/esters, organotrifluoroborates, and 9-borabicyclononane (9-BBN). Organosilicon species were found to undergo cross-coupling reactions with the addition of fluorides by Hiyama.[22]

Scheme 4. Development of cross-coupling reactions with selected examples

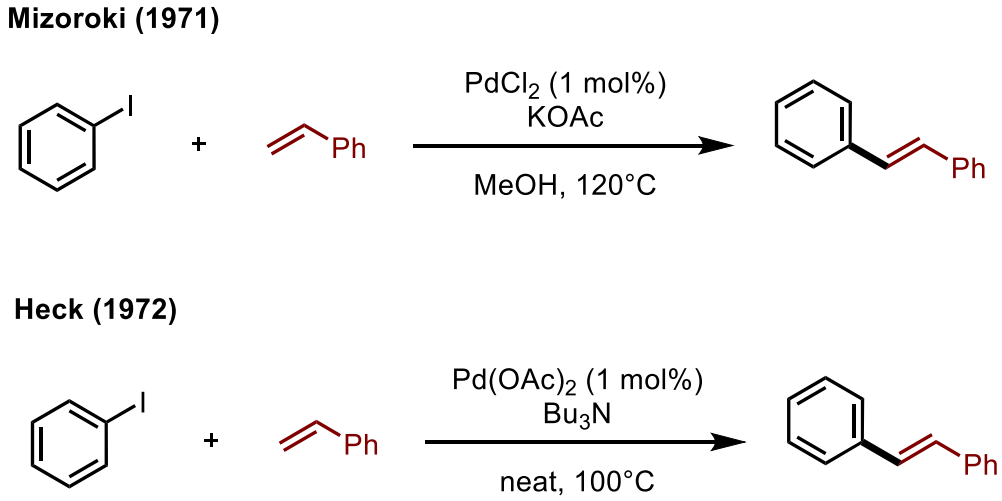


Besides the formation of C—C bonds, cross-coupling reactions can be applied to building C—X bonds. One of the well-developed reactions called the Buchwald-Hartwig amination, can construct new C—N bonds from aryl halide and primary/secondary amines with palladium catalysts.[23,24] Apart from traditional cross-coupling reactions, the nucleophilic coupling partner is an amine instead of carbon-based nucleophiles. One of the requirements in C—N cross-coupling reactions is the use of bulky ligands in suppressing side reactions. In the early years of the cross-coupling development, readily available triphenylphosphine (PPh_3) was the ligand of choice for a long time before people started to recognize the role of ligands in catalysis. During the development of robust and efficient amination conditions, ligand design can prevent side pathways in catalysis and expand the scope of the reaction. For instance, Buchwald and co-workers designed a highly modular ligand class called the biaryl phosphine ligands that have now developed into a widely-used ligand class active in many metal-catalyzed C—N and C—C bond-forming reactions.[25] One of the research trends nowadays in cross-coupling reactions is to design and explore the ligand as potential solutions for new reaction discovery and for accessing synthetically challenging cross-coupled products.

1.2 Mizoroki-Heck reaction

As mentioned earlier, Mizoroki and Heck independently discovered the arylation of terminal alkenes by using palladium-catalyzed conditions. Both of the seminal reports claimed styrenes are able to couple with aryl iodides in the presence of a base and catalytic amount of palladium to give trans-stilbene products (Scheme 5).[12,13] The detailed study of this reaction was later pioneered by Richard F. Heck and it is known nowadays as the Mizoroki-Heck reaction or the Heck reaction.

Scheme 5. Initial reports of the Mizoroki-Heck reaction



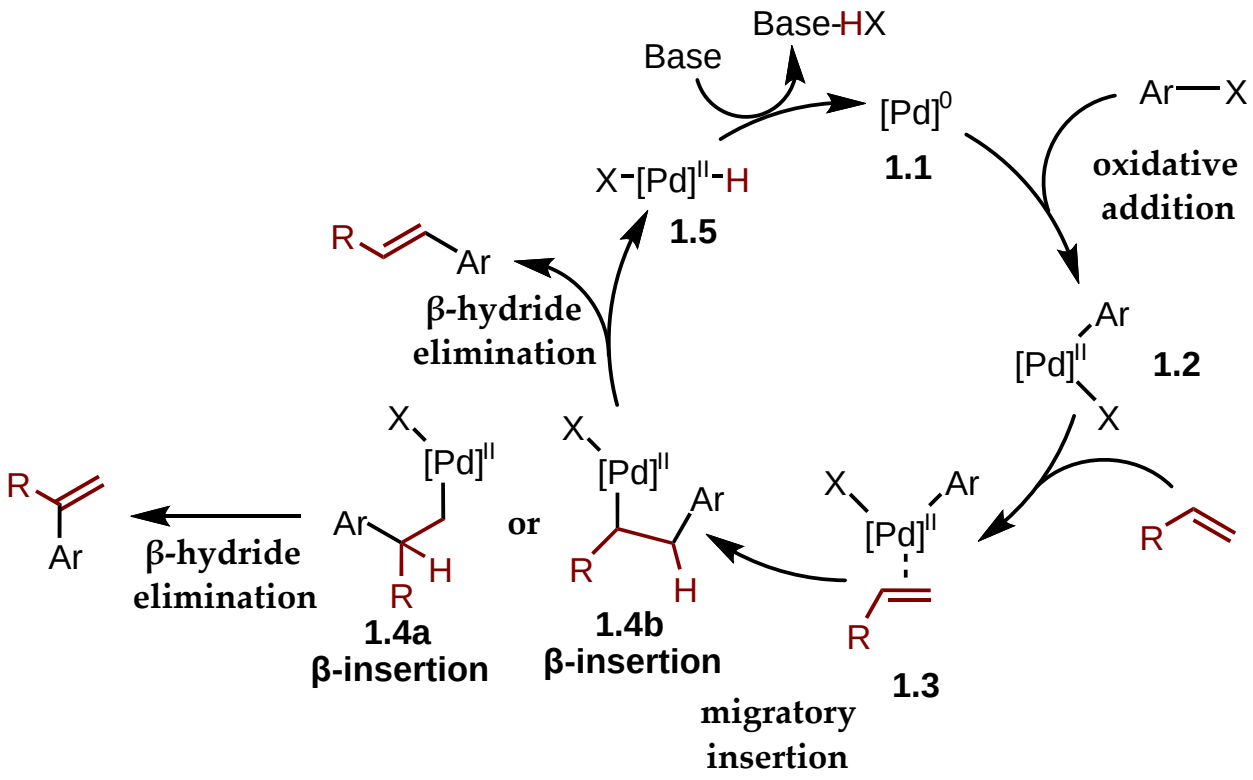
1.2.1 Mechanism of Mizoroki-Heck reaction

The Mizoroki-Heck reaction is a unique class in the cross-coupling reactions as it doesn't follow the mechanism shown in Scheme 2. The mechanism of a Heck reaction is illustrated in Scheme 6.[26] Same as the other cross-coupling reactions, the first step is still oxidative addition of the aryl halide to the Pd(0) complex (**1.1**) to generate intermediate complex **1.2**. Differing from the previous case, no organometallic reagents are used in the Heck reaction, thus the transmetallation is absent in the mechanism. Instead, the alkene

can interact with the palladium complex and insert into the Pd-C_{aryl} bond by an elementary step called migratory insertion. During this step, the olefin coordinates to the palladium center first (**1.3**) and then undergoes a syn insertion to yield carbopalladation product **1.4**. This is the regio-determining step in the Mizoroki-Heck reaction, in which two regioisomers (**1.4a** and **1.4b**) are possible. Both complexes can undergo β-hydride elimination to release the arylated alkene product. This step requires palladium and the eliminated hydrogen to be *syn* across the C—C bond. Usually, the free C—C bond rotation can bring the β-hydrogen *syn* to the palladium. However, if the C—C bond is unable to rotate to the correct position, the reaction would not be able to give any Heck products. At the end of the cycle, the palladium hydride species **1.5** could undergo a reductive elimination mediated by a base to regenerate the Pd(0) species **1.1**.

In principle, three products (α-product, *cis*-β-product, and *trans*-β-product) could form during a Mizoroki-Heck reaction. In practice, the *cis*-β-product is rarely observed in significant amounts. Although the *cis* product has a chance to form during the reaction, it would readily reinsert back to the palladium center as the β-hydride elimination is reversible, consequently isomerizing into the thermodynamic *trans* product. However, on the other hand, the formation of α and β Heck products can be controlled by the selection of starting materials and the catalyst. This topic will be discussed in detail in the following section.

Scheme 6. Mechanism of Mizoroki-Heck reaction

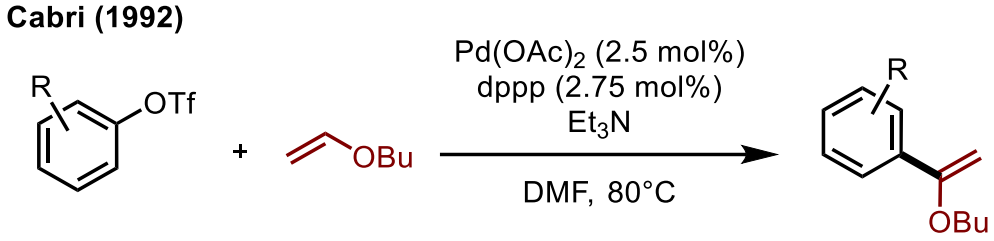


1.2.2 Regioselectivity of Mizoroki-Heck reaction: with a focus on α-selective reactions

In their initial discoveries, both Mizoroki and Heck reported the *trans*-β-product as the major product when styrene and methyl acrylate. This has been found to be the common regioselectivity in traditional Mizoroki-Heck reactions with electron-poor alkenes. This result was attributed to less steric interaction to install an aryl group on the less substituted carbon. However, the electronic factor on regioselectivity was also realized later. Heck noticed that some electron-rich alkenes give a mixture of α and β isomers; nevertheless, steric effects generally dominate.[27] However, even though the arylation on the α-position has been observed as a part of the mixture, it was found difficult to push the selectivity towards this end. The α-selective Heck reaction only

became possible at the beginning of the 1990s due to the use of pseudohalides in cross-coupling. In 1992, Cabri and co-workers discovered an α-selective arylation of vinyl ethers (Scheme 7).[28] The key of this selectivity is to use aryl trifluoromethanesulfonate (triflate, OTf) as the electrophile in the cross-coupling. Using aryl iodides or bromides yields a mixture unless to use a halide scavenger is employed. To explain this, they proposed that a Heck reaction can undergo either of two pathways, namely the neutral route and the cationic route (Scheme 8).

Scheme 7. Cabri's α-selective arylation of vinyl ethers



After oxidative addition, a cationic π-complex can be generated as the triflate group can easily dissociate from the palladium center,[29] allowing the mechanism to switch to the cationic route. The cationic mechanism favors aryl group migration to the α-carbon because of the lower electron density with respect to the β-carbon and a strongly polarized system can overcome the steric effect. In the neutral mechanism as in many of the traditional Heck conditions with aryl halides, the steric effect dominates and provides the β-product. It should be noted that the use of a bidentate ligand is shown to facilitate the cationic route as it saturates the coordination around palladium to prevent the anions from coordinating. In contrast, monodentate phosphines are better performing than bidentate phosphine ligands in the neutral route due to the requirement to constantly dissociate from the palladium.[27]

Scheme 8. Neutral route and cationic route in the Heck reaction

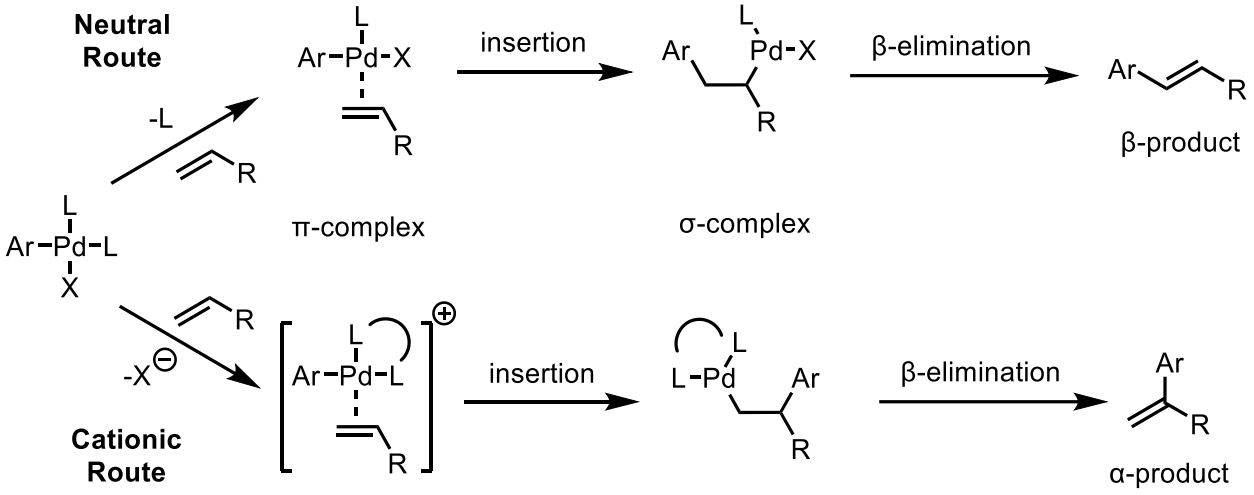
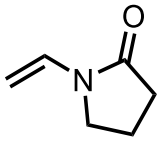
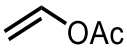
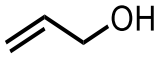
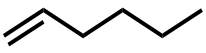
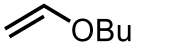


Table 1. Screening experiment of neutral vs cationic mechanism by Cabri

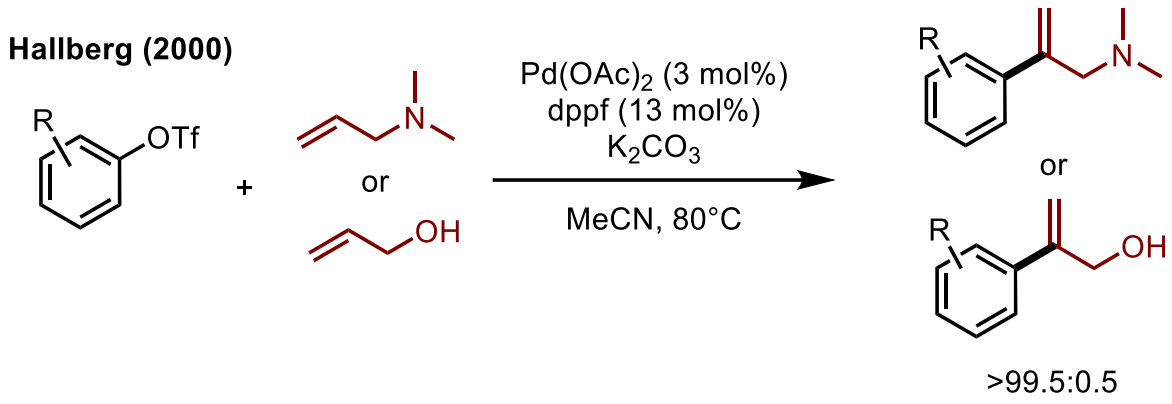
Alkenes	Neutral		Cationic	
	α	β	α	β
	0	100	40	60
	40	60	100	0
	mixture of products		95	5
	0	100	100	0
	20	80	80	20
	mixture of products		100	0

This mechanism-determined regioselectivity was also supported with a screening test by Cabri.[30] As listed in Table 1, the arylation outcomes are greatly influenced in terms of the regioselectivity by switching into the cationic mechanism. Electron-rich and electron-neutral alkenes demonstrated a complete switch in regioselectivity from β to α.

For styrenes, although the β-product is still in majority, a significantly amount of α-product was formed when cationic conditions were applied.

Realization of the cationic mechanism in the Mizoroki-Heck reaction has opened up the door to develop α-selective arylations. Hallberg and co-workers demonstrated that a highly α-selective Heck reaction could be achieved with allylic amine and alcohol (Scheme 9).[31] The high regioselectivity was found to be not only contributed by the mechanism but also by coordination of nitrogen or oxygen to the palladium. A control experiment was conducted without the nitrogen atom in the alkene and the regioselectivity was shown to be significantly reduced.

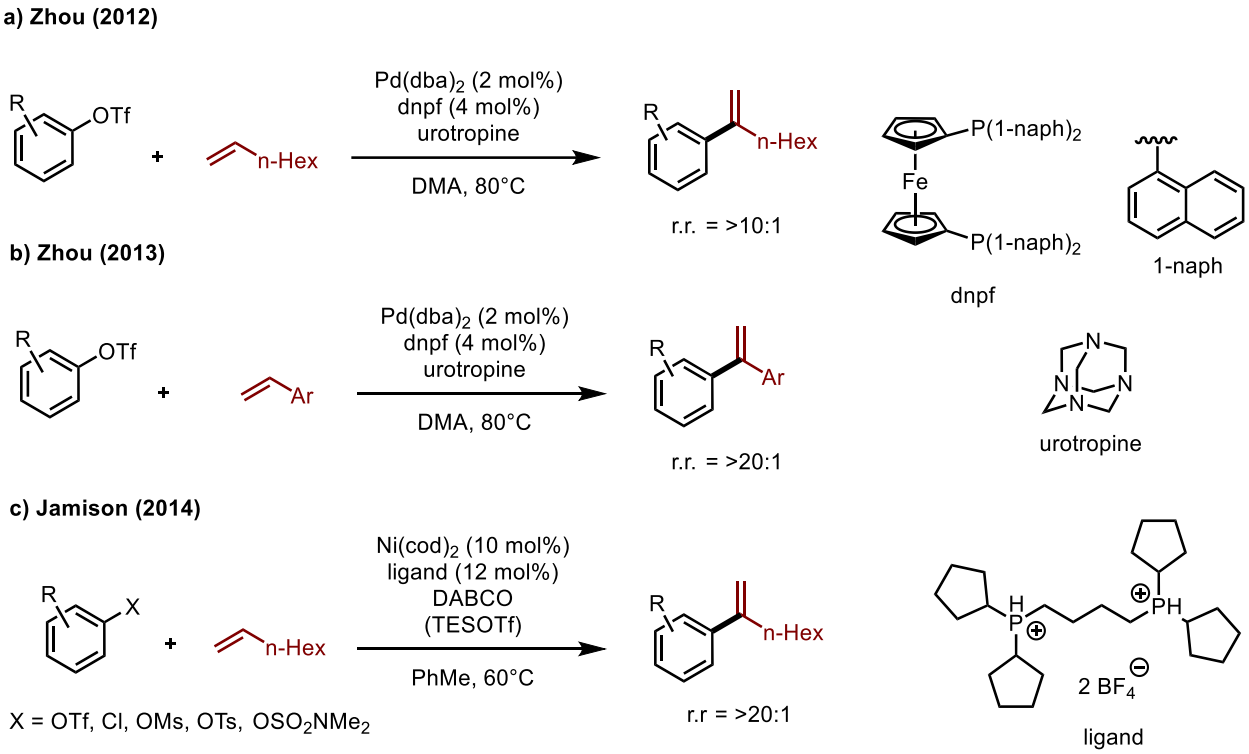
Scheme 9. Hallberg's highly α-selective arylation of allylic amine and alcohol



For unbiased or electron-poor alkenes, the α-selectivity is more challenging since some extra controls are needed other than the cationic mechanism to push the regioselectivity. In 2012, Zhou and colleagues reported an α-selective arylation of aliphatic olefins[32] (Scheme 10a) and they were able to expand the scope to styrenes shortly after[33] (Scheme 10b). In both reports, aryl triflates were employed to allow the reaction to undergo the cationic mechanism. The key factor in determining the regioselectivity is the use of ferrocene-based bisphosphine ligands. Among all the ligands examined, 1,1'-bis[di(1-naphthyl)phosphino]ferrocene (dnpf) showed the best regioselectivity and

reactivity. The authors conducted X-ray studies on the Pd(dnpf) complex and DFT calculations on the insertion step, and they proposed that the steric bulk caused by the ligand around the palladium center would disfavour terminal insertion over internal insertion. The selection of base was also shown to have an impact on the formation of the desired product. The use of common organic bases such as triethylamine and Hunig's base was shown to reduce the aryl triflates to arenes similar to those previously reported.[34] Urotropine, also known as hexamethylenetetramine, was identified as the base to avoid reduction and facilitate the desired Heck reaction. In 2014, the Jamison group reported a nickel-catalyzed α-selective Mizoroki-Heck reaction of aliphatic olefins[35] (Scheme 10c). Aryl triflates are effective in this chemistry as the cationic mechanism is still required in Ni catalysis. Bidentate phosphine ligands were shown to provide good conversion and regioselectivity, and they identified a bidentate cyclopentyl bis(phosphine) as the optimal ligand. Due to the use of nickel, which can activate more inert bonds in oxidative addition, this reaction can also be applied to aryl chlorides, mesylates, tosylates, and sulfamates with the addition of a counterion exchange reagent TESOTf to maintain the cationic mechanism.

Scheme 10. Examples of α-selective arylation of aliphatic olefins and styrenes



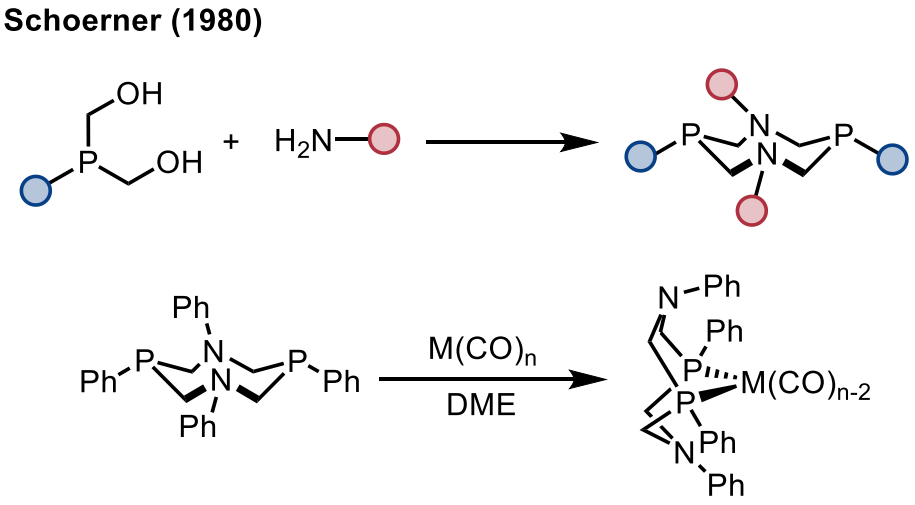
1.3 P_2N_2 ligands in transition-metal catalysis

1.3.1 General considerations of P_2N_2 ligands

The success of transition-metal catalysis would not be possible without the extensive study on ligands, which are responsible for tuning the characteristics of metals and achieving the desired chemical transformation. As one of the ligand classes designed for transition-metal catalysis, 1,5-diaza-3,7-diphosphacyclooctane compounds, commonly referred to as P_2N_2 nowadays, were first disclosed and synthesized by Schoerner and co-workers[36] in 1980 (Scheme 11). Coordination complexes of nickel and molybdenum with P_2N_2 ligands were also included in this initial report, illustrating the bidentate binding mode through the two phosphorus atoms. The eight-membered ring

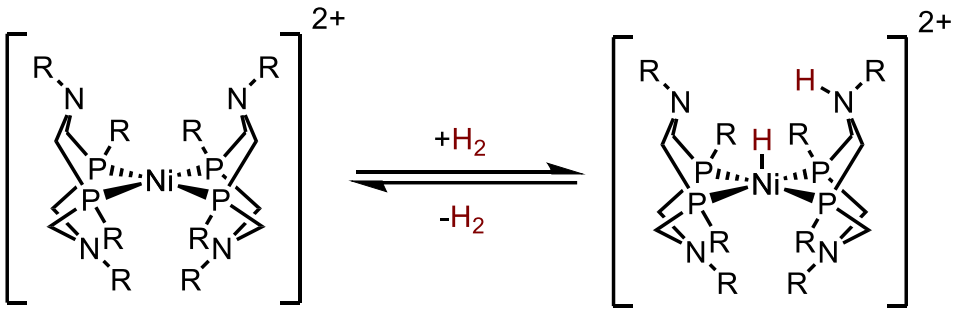
structure is found to be easily constructed by intermolecular phospha-Mannich reaction with equimolecular $RP(CH_2OH)_2$ and primary amine.[37]

Scheme 11. First report of P_2N_2 ligands and the corresponding transition-metal complexes



Due to a variety of primary phosphines (precursor to $RP(CH_2OH)_2$) and primary amines being available commercially or synthetically, a wide range of P_2N_2 ligands have been synthesized and employed in transition-metal catalysis. One of the established applications of P_2N_2 ligands is in the electrocatalytic splitting and production of hydrogen gas with metal-bis(P_2N_2) complexes.[38] In particular, the $[Ni(P_2N_2)_2]^{2+}$ system has been studied extensively regarding this transformation. As shown in Scheme 12, the key dihydrogen splitting/forming step is illustrated, in which the pendant amine group on the P_2N_2 ligand can abstract the proton as it has suitable basicity and is properly positioned relative to the nickel center.

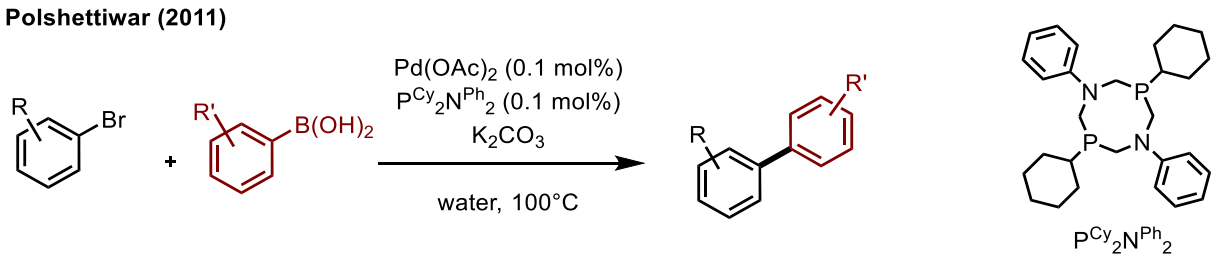
Scheme 12. Illustration of dihydrogen splitting/forming with $[Ni(P_2N_2)_2]^{2+}$



1.3.2 Transition-metal catalyzed organic transformations with P_2N_2 ligands

Despite the success in electrocatalytic oxidation and reduction, only a handful of organic transformations have been reported with P_2N_2 ligands. A short report emerged in 2011 claiming a P_2N_2 ligand is effective in Pd-catalyzed Suzuki-Miyaura coupling in aqueous condition[39] (Scheme 13). However, no control experiments or mechanistic investigations were conducted by the authors. The use of P_2N_2 ligands in cross-coupling reactions and carbon—carbon bond formations has not been further explored until very recently.

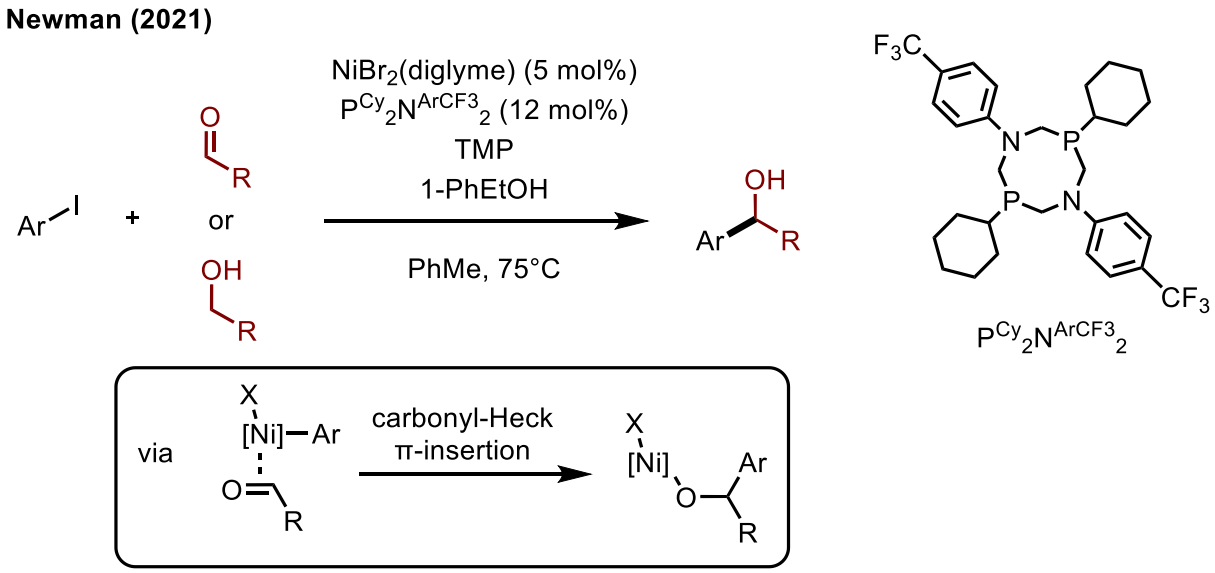
Scheme 13. Pd/P_2N_2-catalyzed Suzuki-Miyaura reaction



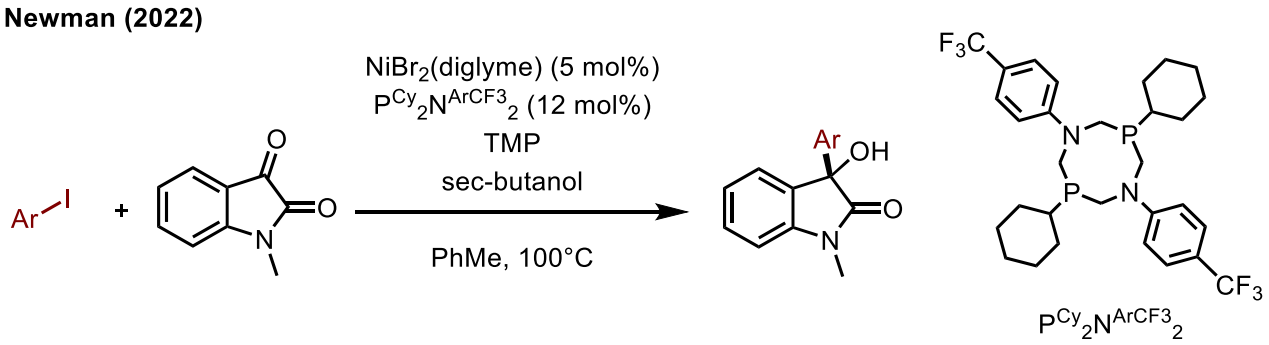
In 2021, Newman and co-workers reported a Ni/P_2N_2-catalyzed reductive arylation of aldehydes and redox-neutral α-arylation of alcohols[40] (Scheme 14). The authors identified $P^{Cy}{}_2N^{ArCF3}{}_2$ as the optimal ligand to facilitate the key carbonyl-Heck

insertion step and avoid the deleterious reduction of aryl halides from Ar—[Ni]—X species. Commercially available monodentate, bidentate phosphines and NHC ligands all showed no desired reactivity as a result of this aryl halide reduction. The 1-phenylethanol additive acts as a mild organic reductant when aldehydes are subjected to the reaction. This catalytic system was further explored with the reduction of isatins to access 3-hydroxy-2-oxindoles with a slightly modified condition but still follows the same mechanism[41] (Scheme 15). The arylation is exclusively found on the carbonyl of the ketone instead of the amide.

Scheme 14. Ni/P_2N_2-catalyzed arylation of aldehydes and alcohols

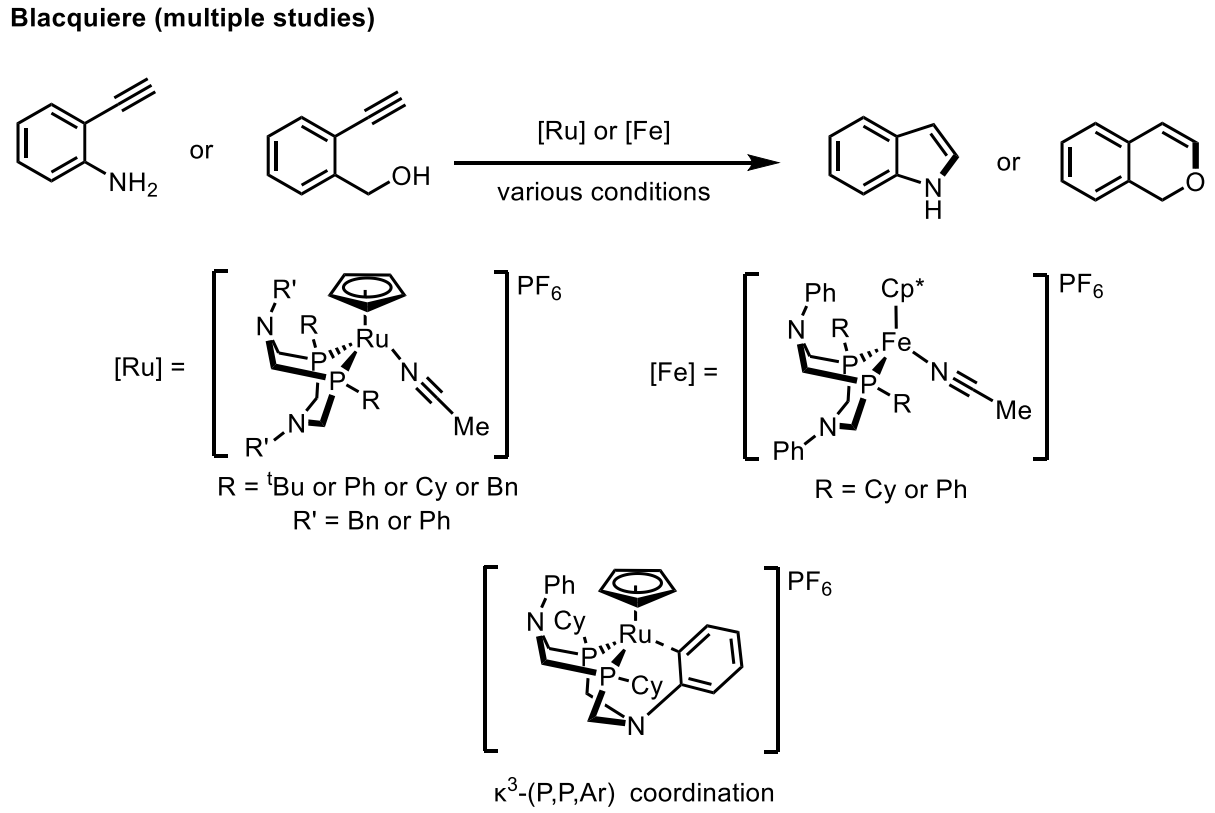


Scheme 15. Ni/P_2N_2-catalyzed selective arylation of isatins



Blacquiere and coworkers in the past few years have published several reports on Ru/P_2N_2 and Fe/P_2N_2 catalyzed intramolecular alkynyl-alcohol and alkynyl-amine cyclizations[42–44] (Scheme 16). Multiple P_2N_2 ligands were found to be effective in this transformation and an exogenous base was not needed due to the basicity of the pendant amine. Detailed studies on the ruthenium system[43] have shown that the ruthenium metal center is stabilized via a κ^3-(P,P,Ar) coordination of the $P^{Cy}{}_2N^{Ph}{}_2$ ligand, similar to the metal-arene interactions of biaryl phosphine ligands in palladium catalysts.[25]

Scheme 16. Ru/P_2N_2 and Fe/P_2N_2 catalyzed intramolecular alkynyl-alcohol and alkynyl-amine cyclization

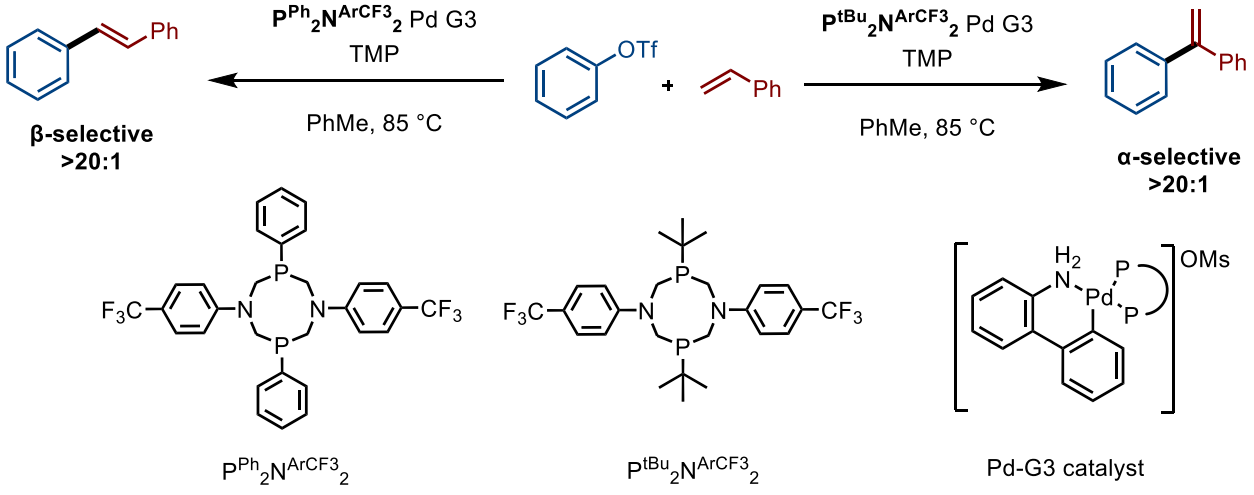


1.3.3 P_2N_2 ligands in Mizoroki-Heck reaction

Due to the analogous insertion step in Ni-catalyzed aldehyde arylation reactions,

the P_2N_2 ligands were envisioned by our group to be applicable in the traditional Mizoroki-Heck reactions. Our lab has realized that the P_2N_2 ligands are not only effective in Pd-catalyzed Heck reactions but also capable of determining the regiochemical outcome of the product.[45] Starting from a high-throughput study, the authors identified two P_2N_2 ligands, $P^{Ph}{}_2N^{ArCF3}{}_2$ and $P^{tBu}{}_2N^{ArCF3}{}_2$, that could yield linear (β) and branched (*α*) Heck product with high regioselectivity, respectively (Scheme 17). Aryl triflates were found to be the only aryl halide/pseudohalide to show reactivity in both of the two Pd-catalyzed reactions. This also marked the first β-selective Heck reaction with aryl triflates and styrenes. A range of styrenes were capable of producing both *α* and β arylation products smoothly under the two reported conditions. DFT calculations provided a hypothesis for the observed regioselectivity. The Pd/$P^{Ph}{}_2N^{ArCF3}{}_2$ system is found to stabilize the β-insertion pathway with a π-π interaction between the P-Ph moiety and the incoming styrenes. However, the $P^{tBu}{}_2N^{ArCF3}{}_2$ ligand is not capable of providing this π-π interaction and is experiencing severe steric clash in the β-insertion pathway, hence the *α*-insertion is favored.

Scheme 17. Pd/P_2N_2 catalyzed regioselective Mizoroki-Heck reaction



1.4 Research goals

After the discovery of the regioselective Mizoroki-Heck reaction with the Pd/P_2N_2 system described in Scheme 17, we wanted to expand this reaction towards a broader scope beyond alkenes and ideally provide novel and efficient synthetic methods for accessing synthetically challenging compounds. We also believed that expanding the breadth and generality of highly regioselective Mizoroki-Heck reactions was needed to make the reaction more applicable in the synthesis of pharmaceutical products and other important molecules. Heck reaction is much less used than many other cross-coupling and carbon—carbon bond-forming reactions in the synthesis of medicinal compounds although it has been extensively studied in academia.[46]

The overarching goal of this thesis was to develop a regioselective Heck reaction that enabled the synthesis of α-substituted vinylboron compounds from vinylboronates. As alkenyl boron compounds are widely used building blocks in synthetic chemistry, we envisioned that we could provide an efficient method to have access to alkenyl boron compounds with readily available starting materials and a Pd/P_2N_2 catalyst. In Chapter 2, our efforts towards this goal are described, ultimately leading to the synthesis of α-vinylboronates through a regioselective Mizoroki-Heck reaction. We hope this will further explore the potential of the Pd/P_2N_2 catalyst and bring the P_2N_2 ligands into the toolbox of synthetic chemists.

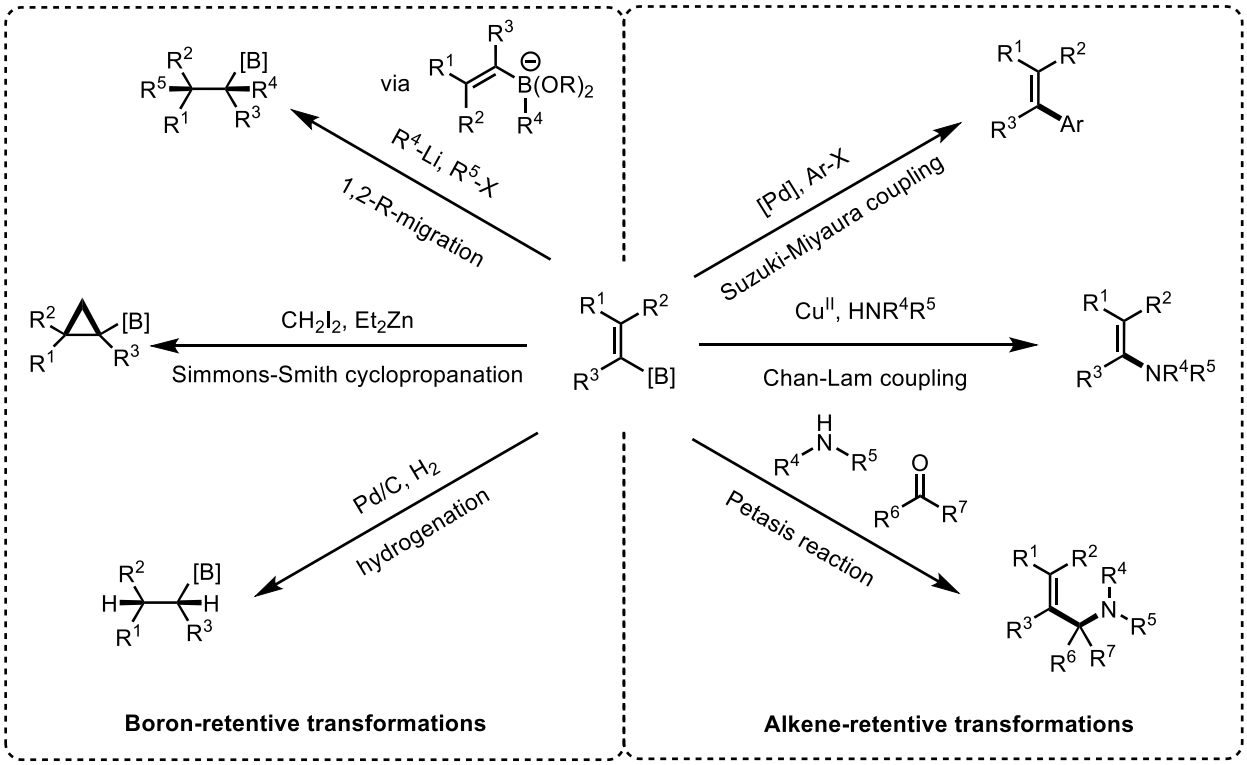
Chapter 2 Highly Regioselective Synthesis of α-Vinylboronates via a Pd-Catalyzed Mizoroki-Heck Reaction

2.1 Background

2.1.1 Alkenyl boronates: applications and synthesis

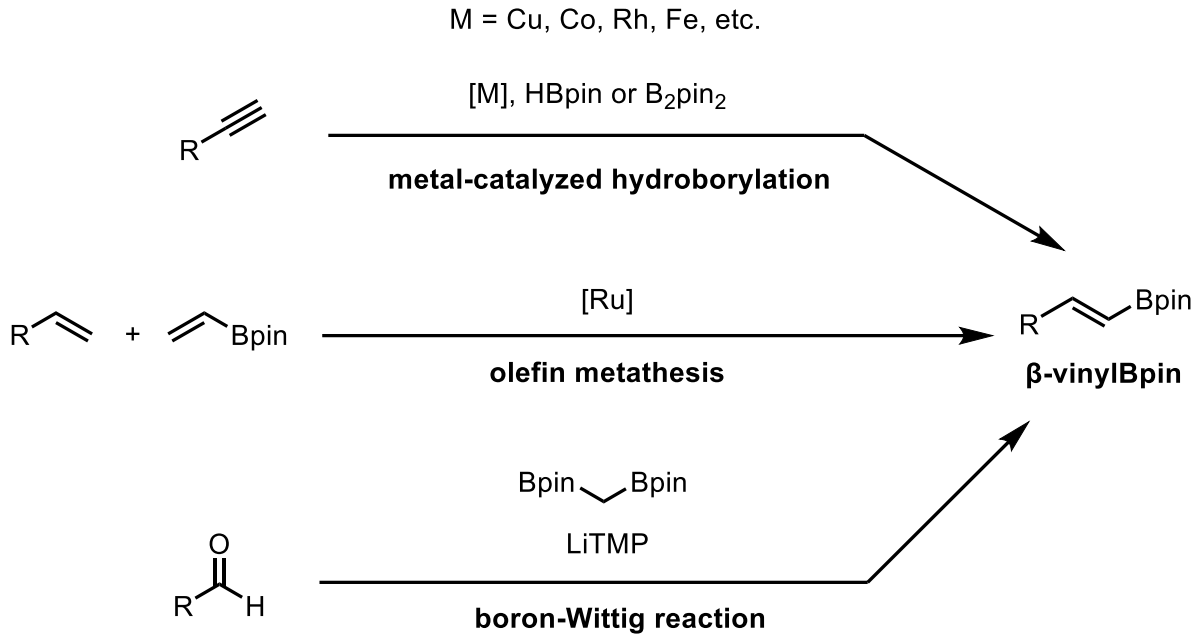
Since the discovery of the Suzuki-Miyaura coupling, organoboronic acids and organoboronic esters (organoboronates) have gained a lot of attention and are used widely by synthetic chemists as versatile reagents in connecting carbon—carbon bonds and building complex molecules. Compared to aryl and alkyl boronates, alkenyl boronates (or vinylboronates) can add another level of reactivity as the olefin could also be involved in the reaction, resulting in much broader reaction types and products.[47] As shown in Scheme 18, alkenyl boronates can undergo a wide spectrum of alkene-retentive transformations such as Suzuki-Miyaura,[21] Chan-Lam coupling,[48] and Petasis reaction.[49] Vinylboron compounds are commonly used to efficiently construct new C—X and C—C bonds via 1,2-alkyl/aryl migrations of vinylboron ate complexes, as pioneered by Zweifel,[50] Morken,[51] Studer,[52,53] and Aggarwal.[54] Some other boron-retentive reactions such as cyclopropanation[55] and Pd/C hydrogenation[56] could also be achieved with vinylboron starting materials. One can imagine further diversifications to construct more complex molecular targets from these products due to the presence of reactive functional groups.

Scheme 18. Selected transformations of alkenyl boronates



Therefore, as a result of realizing these highly useful building blocks in organic synthesis, the synthesis of alkenyl boronates has been pursued by synthetic chemists. For disubstituted vinylboronates, many synthetic methods have been developed to synthesize the β-vinylboronic pinacol ester (β-vinylBpin), including the hydroboration of terminal alkynes,[57] olefin cross-metathesis,[58] and boron-Wittig reactions[59] (Scheme 19). However, the synthesis of α-vinylboronates is less explored, presenting challenges associated with controlling the regioselectivity towards the more substituted side. A detailed discussion on the preparation of α-vinylboronates will be given in section 2.1.2.

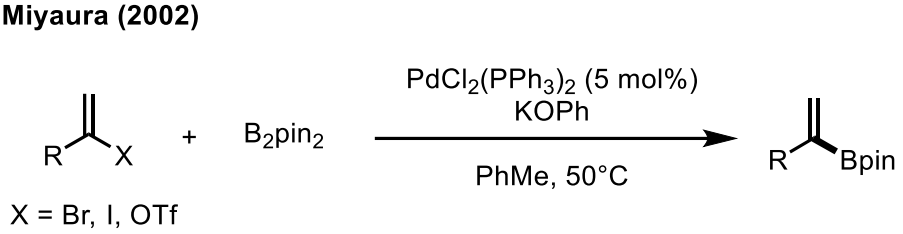
Scheme 19. Selected preparation of β-vinylBpin



2.1.2 Literature review on the synthesis of α-vinylboronates

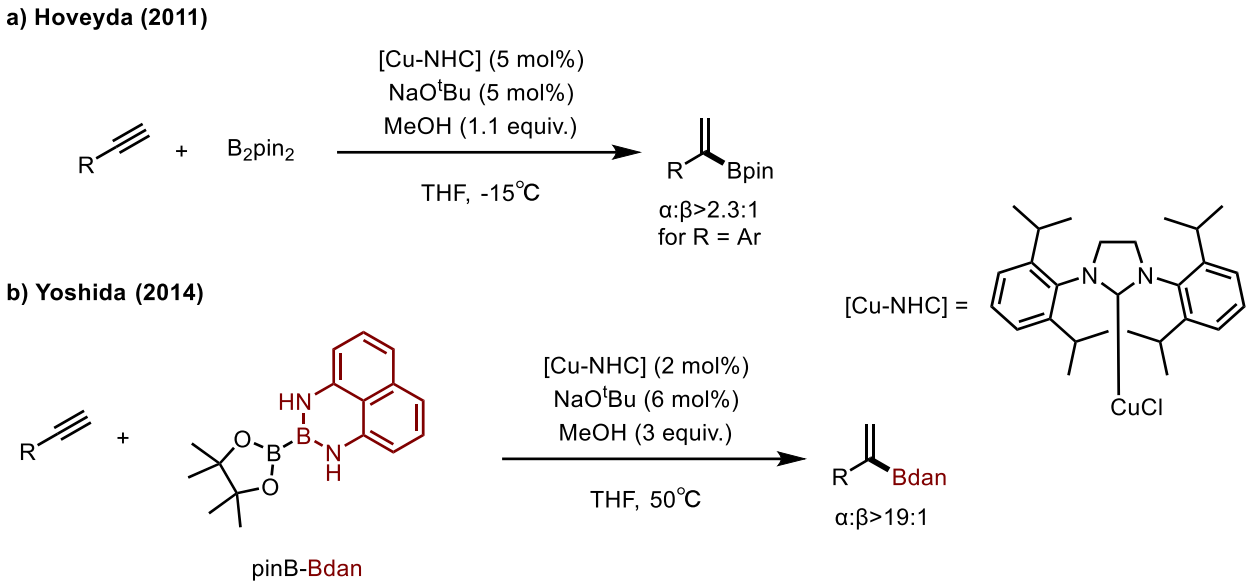
Unlike for β-vinylboron compounds, the preparation of α-vinylboronates suffers from several challenges including the borylation towards the more sterically hindered side of the alkyne. Moreover, reaction methodology is limited as some reactions can only construct the β geometry such as olefin cross-metathesis. In the early 2000s, Miyaura and co-workers reported the synthesis of α-vinylboronic acid pinacol esters (α-vinylBpin) via a Pd-catalyzed borylation of α-vinylhalides[60] (Scheme 20). While this provides a robust method to synthesize α-vinylboronates without the concern of regioselectivity, the α-vinylhalides have to be prepared from the corresponding alkynes and one has to control the regioselectivity in the hydrohalogenation reaction.[21]

Scheme 20. α-vinylboronate synthesis via Pd-catalyzed Miyaura borylation



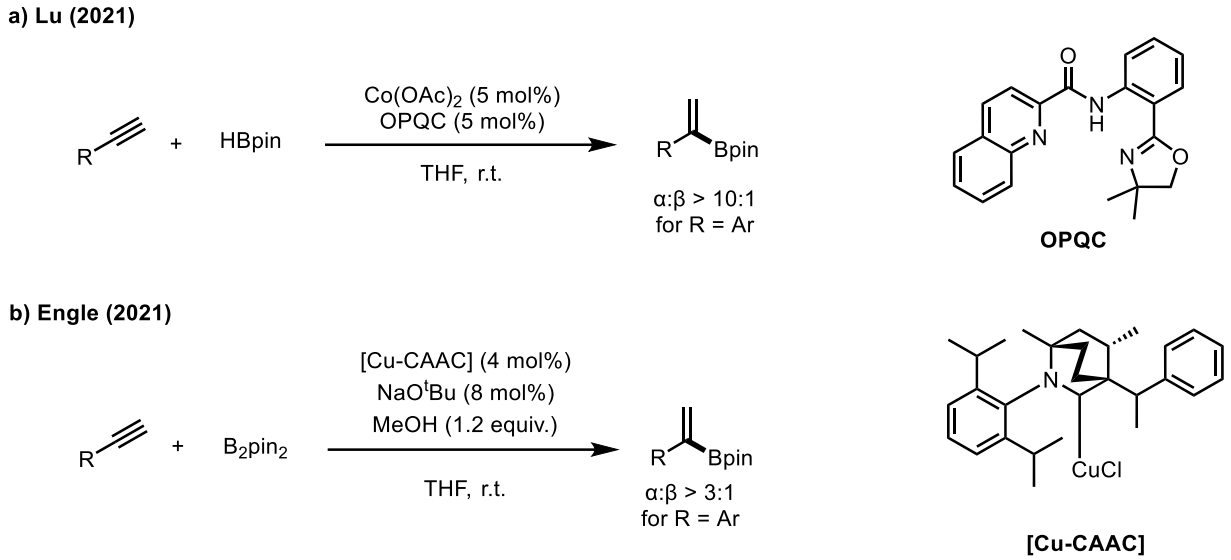
In recent decades, metal-catalyzed hydroboration of alkynes with regioselective control has been developed to provide a more efficient strategy to synthesize α-vinylboronates. In 2011, the Hoveyda group reported the first α-selective hydroboration of alkynes using a copper-NHC complex[61] (Scheme 21a). The authors identified the sterically demanding SIPr or SIMes ligand to favor the α-borylation. This method can achieve excellent regioselectivity with propargyl alcohols and amines; however, aromatic alkynes generally exhibit lower selectivity which is diminished further with ortho-substituted substrates. Yoshida achieved improved yield and selectivity using a mixed diboron compound pinB-Bdan[62] (Scheme 21b). However, this report only covers a small range of alkyl and aryl alkynes. The 1,8-diaminonaphthalene (dan) protecting group for boron is present also in the final product, which requires an extra step to transform it into a boronic acid pinacol ester (Bpin) for further functionalization.

Scheme 21. α-vinylBpin synthesis via Cu/NHC-catalyzed hydroboration of alkynes



Recently, Lu[63] and Engle[64] demonstrated that α-selective hydroboration can also be achieved with Co (Scheme 22a) and Cu/CAAC (Scheme 22b) systems. In both reported reactions, the selection of ligand is crucial to achieve this stereoselectivity. Lu and colleagues screened eight N,N,N-tridentate ligands and found that N-(oxazolinylphenyl)quinoline-2-carboxamide (OPQC) is able to provide the best regioselectivity with the Co catalyst. They demonstrated that aryl substrates can undergo this transformation with >10:1 α:β ratio. The Engle lab identified one of the cyclic(alkyl)(amino)carbene (CAAC) ligands among six synthesized CAAC ligands in their copper-catalyzed condition. At the same time, aryl substrates showed lower regioselectivity compared to their alkyl examples. In both reports, the ligand is the key for regiocontrol; however, both ligands are not readily available and require multiple steps to synthesize.

Scheme 22. Recent developments in the synthesis of α-vinylBpin via metal-catalyzed hydroboration



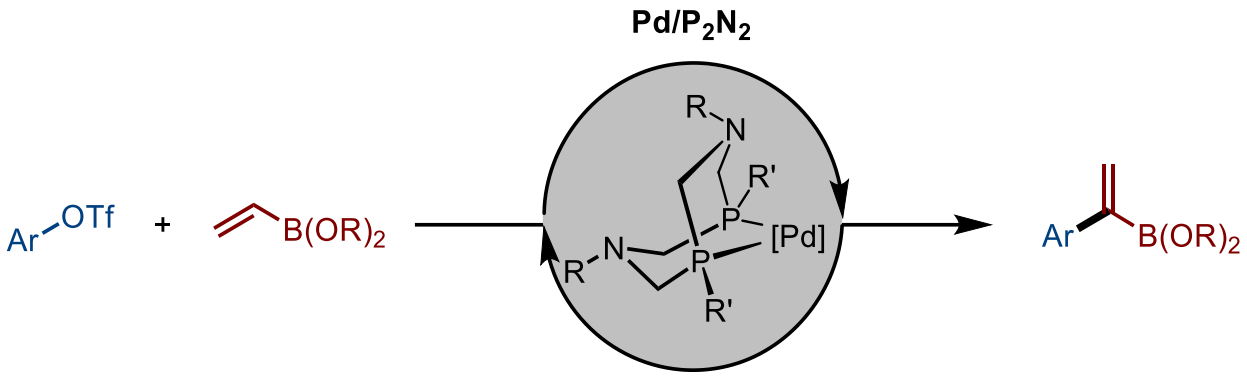
2.2 Pd/P_2N_2-catalyzed regioselective Mizoroki-Heck reaction of vinylboronates

2.2.1 Project design

The Heck reaction of vinylboron compounds has precedence in the literature; however, all reported examples only yield the β-Heck product and the α-product was never mentioned.[65–69] In addition, direct synthesis of α-vinylboronates has not been achieved from a boron-containing substrate. Given the challenges in the synthesis of α-vinylboronates as mentioned above, we hypothesized that the Pd/P_2N_2 system developed by our lab could be used to provide a solution by involving aryl triflates and vinylboronates in the reaction (Scheme 23). We thought that this would be a more advantageous method compared to the strategies mentioned above since the tunable Pd/P_2N_2 catalysts can be readily prepared in a large scale without any complications in

the work-up.

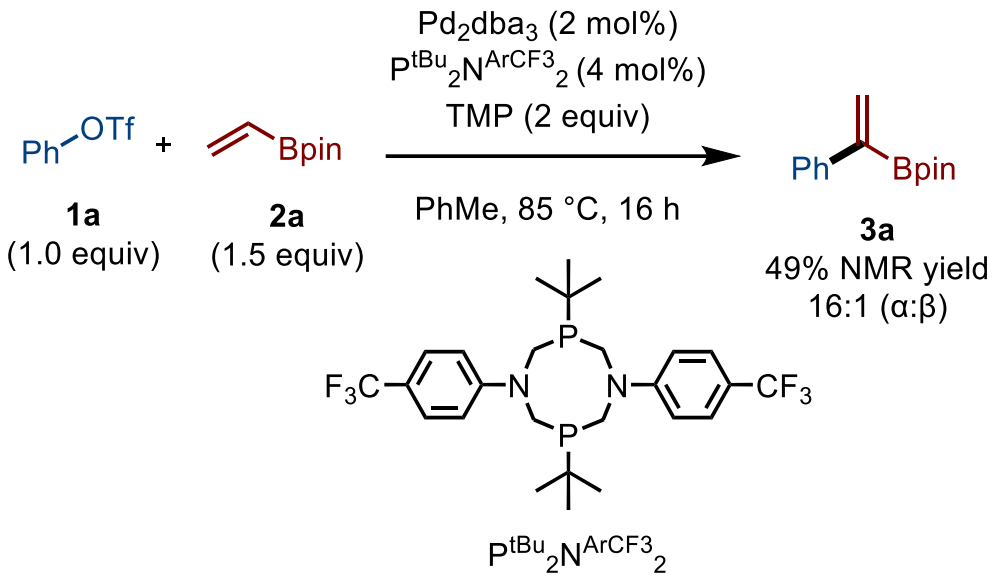
Scheme 23. Research project: Synthesis of α-vinylboronates via Pd/P_2N_2-catalyzed Mizoroki-Heck reaction



2.2.2 Initial reaction discovery and optimization

This project began by testing the desired transformation with phenyl triflate (**1a**) and vinylBpin (**2a**) in a Pd/P_2N_2 catalytic system that is active in the α-arylation of styrenes.[45] As shown in Scheme 24, the coupling reaction was carried out in the presence of 2 mol% of tris(dibenzylideneacetone)dipalladium (Pd_2dba_3), 4 mol% of the P_2N_2 ligand, 2 equivalents of 2,2,6,6-tetramethylpiperidine (TMP) base, in toluene solvent at 85°C for 16 hours.

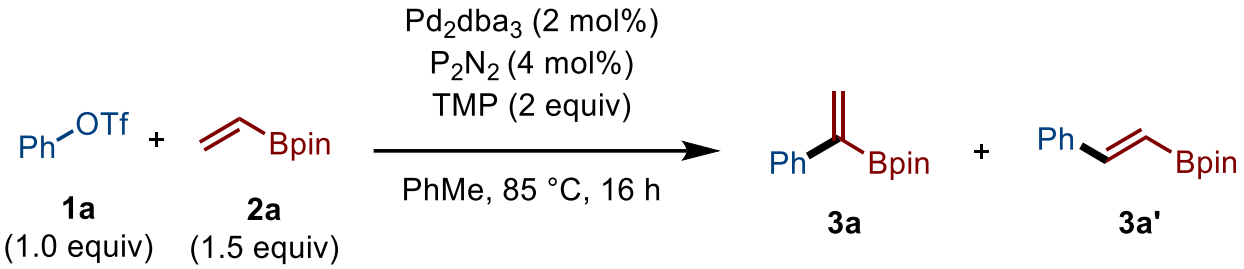
Scheme 24. Initial reaction discovery with phenyl triflate and vinylBpin

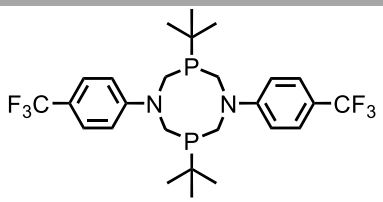
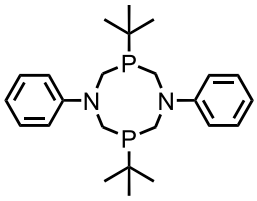
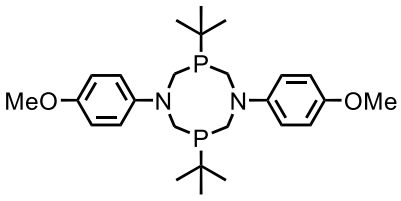


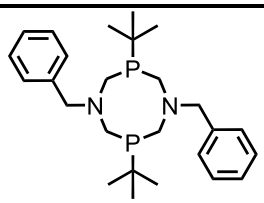
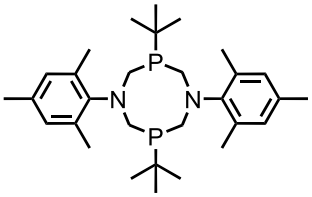
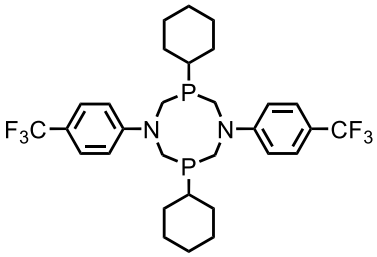
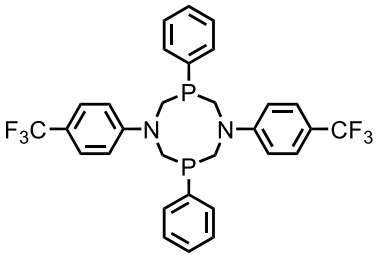
To our delight, this condition afforded the desired α-arylation product in 49% yield with a 16:1 regiomeric ratio (determined by NMR). With this initial hit, we then tested how other P_2N_2 ligands would perform under the listed conditions. As shown in Table 2, among the seven selected P_2N_2 ligands, $P^{tBu}{}_2N^{ArCF3}{}_2$ demonstrated the best reactivity and regioselectivity toward the desired α-product. Switching the substituent on both of the phosphorus and nitrogen can have significant effects on the results. Increasing the electron-donating ability of the nitrogen substituent led to a significant decrease in both yield and selectivity (entry 2-4). This trend might suggest that the basicity of the pendant amines on the ligand can influence the catalyst performance with the more basic pendant amine forming less of the desired product. However, no direct evidence was found to correlate this basicity with Heck reactivity and further investigation will be needed to gain a better understanding of this observation. This result is consistent, however, with the arylation of aldehydes, in which electron-donating groups on the nitrogen of P_2N_2 could negatively impact the catalytic performance.[40] Use of $P^{tBu}{}_2N^{Mes}{}_2$ completely shut down the reaction, which is possibly due to the increase of

steric bulk around the metal which hinders the substrate from binding (entry 5). Switching the substituent on phosphorus from tert-butyl to cyclohexyl or phenyl group both resulted in no selectivity towards the α-product (entries 6-7). It is worth noting that the $P^{Ph_2}N^{ArCF3_2}$ ligand did not provide high β-selectivity as observed in the coupling of styrenes[45], instead, it gave a 1:1 mixture of both regiomers.

Table 2. P_2N_2 ligand screening for the coupling of phenyl triflate and vinylBpin



entry	P_2N_2 ligands	Yield of 3a	yield of 3a′	α:β ratio
1	 $P^{tBu_2}N^{ArCF3_2}$	49%	3%	16:1
2	 $P^{tBu_2}N^{Ph_2}$	43%	7%	6:1
3	 $P^{tBu_2}N^{ArOMe_2}$	13%	13%	1:1

4	 $P^{tBu}{}_2N^{Bn}{}_2$	5%	6%	1:1
5	 $P^{tBu}{}_2N^{Mes}{}_2$	0%	0%	/
6	 $P^{Cy}{}_2N^{ArCF3}{}_2$	4%	11%	1:3
7*	 $P^{Ph}{}_2N^{ArCF3}{}_2$	22%	22%	1:1

*4-cyanophenyltriflate was used

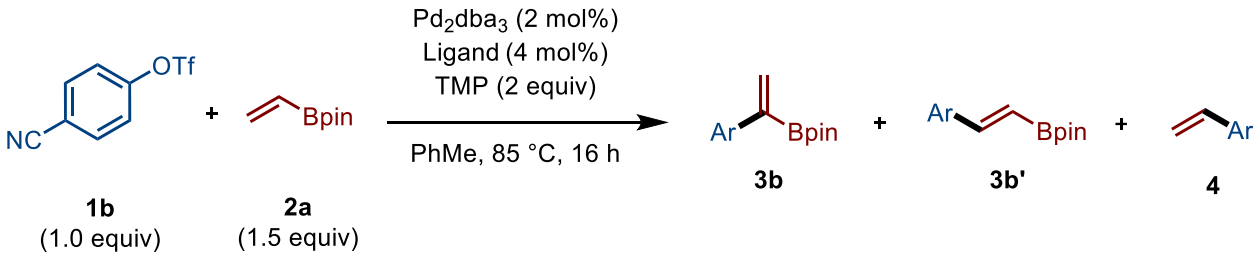
All reactions were conducted at 0.1 mmol scale

All yields were determined by ^{1}H NMR with 1,2,4,5-tetramethylbenzene as the internal standard

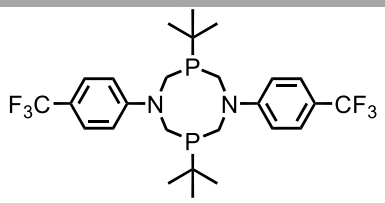
We then compared the best P_2N_2 ligand with some of the commercially available ligands that are commonly used in cross-coupling reactions. It should be noted that we were unable to obtain mass balance in the products when phenyl triflate was used as the

starting material. We believe that styrene was formed in this reaction by a Suzuki pathway, but this product was lost when we prepared the NMR samples in high vacuum due to the volatility of styrene. Therefore, we selected a heavier aryl triflate 4-cyanophenyltriflate as our new model substrate since it allowed us to better track down the products formed. As illustrated in Table 3, the optimal P_2N_2 ligand gave 68% yield of the α-product **3b** and 7% yield of the non-desired β-isomer **3b'**, resulting in a ~10:1 regiomeric ratio (entry 1). By using this substrate, we could now quantify styrene product **4**, which was about 22% when $P^{tBu}{}_2N^{ArCF3}{}_2$ was employed. Ferrocene-based bidentate ligand dppf, which has previously been shown to be effective in some α-selective Heck reactions[31,33], was unable to provide comparable regioselectivity under the listed conditions. Other bidentate phosphine ligands did not result in significant amounts of the desired product (entries 3-6). Buchwald ligands also did not provide any productive results on the formation of **3b** (entry 7-10). Bidentate nitrogen ligands gave some switches in selectivity, with phenanthroline providing only the β-product **3b'** in 60% yield (entry 11) and bipyridine giving more Suzuki product (entry 12). IPr and phosphonium salt ($P^tBu_3{\cdot}HBF_4$) both did not show any Heck reactivity (entries 13 and 14).

Table 3. Commercial ligand screening for the coupling of 4-cyanophenyl triflate and vinylBpin



1b (1.0 equiv) **2a** (1.5 equiv) **3b** **3b'** **4**

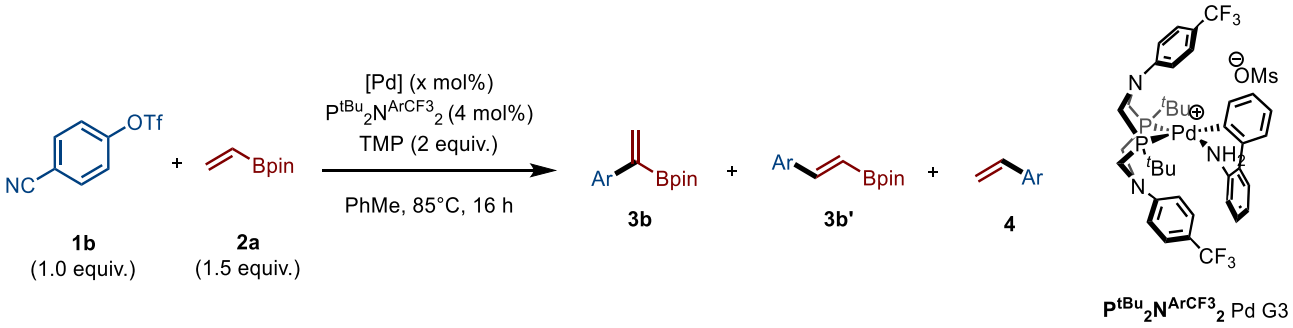
entry	Ligand	Yield of 3b	yield of 3b′	α:β ratio	yield of 4
1	 $P^{tBu}{}_2N^{ArCF3}{}_2$	68%	7%	10:1	22%
2	dppf	43%	13%	3:1	21%
3	dppp	3%	4%	1:1	19%
4	*rac*-BINAP	12%	46%	4:1	24%
5	dcype	0%	0%	/	6%
6	Xantphos	0%	4%	/	3%
7*	SPhos	2%	20%	1:10	7%
8*	XPhos	0%	0%	/	12%
9*	JohnPhos	0%	2%	/	5%
10*	DavePhos	0%	0%	/	8%
11	phenanthroline (phen)	0%	60%	/	19%
12	2,2'-bipyridine (bipy)	0%	9%	/	30%
13*	IPr	0%	0%	/	3%
14*	$P^tBu_3{\cdot}HBF_4$	0%	0%	/	0%

*8 mol% for monodentate ligands
All reactions were conducted at 0.1 mmol scale
All yields were determined by ^1H NMR with 1,2,4,5-tetramethylbenzene as the internal standard

With the optimized ligand in hand, we then turned our goal into optimizing other parameters in the reaction. A range of palladium pre-catalysts was tested in this reaction, as shown in Table 4. Except for the allylpalladium chloride dimer (entry 4), all of the other palladium sources demonstrated comparable reactivity to Pd_2dba_3. Pd(II) pre-catalyst

palladium acetate was also productive in this reaction albeit resulting in a bit higher amount of the Suzuki product (entry 3). This increase in the Suzuki product could be due to the presence of acetate anions, which would act as an inorganic base and promote the Suzuki reaction.[69] The Buchwald Pd pre-catalyst G3 bearing our optimal $P^{tBu}{}_2N^{ArCF3}{}_2$ ligand (**$P^{tBu}{}_2N^{ArCF3}{}_2$** Pd G3) was found to give similar results compared to using Pd_2dba_3 pre-catalyst (entry 2). We decided to use the Pd G3 pre-catalyst in the following studies owing to its better bench stability and reaction consistency.[45] The additional ligand along with the use of Pd G3 increased the yield of **3b** by 3% (entry 5), but we believe this is not significant and still within the error bar of quantitative NMR experiments.

Table 4. Screening of Pd precatalysts for the coupling of 4-cyanophenyl triflate and vinylBpin



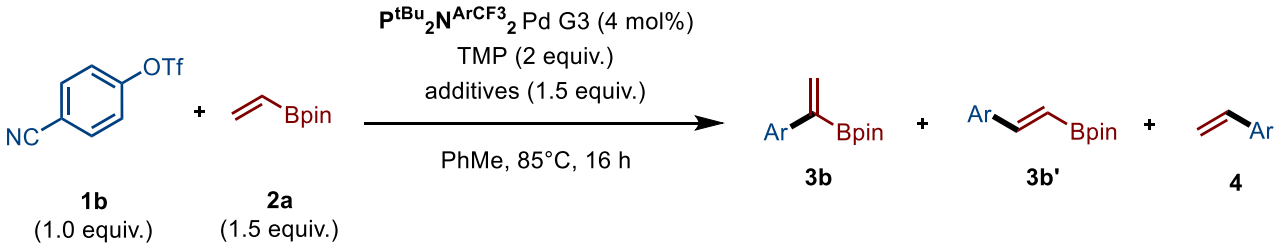
entry	[Pd]	Yield of 3b	yield of 3b′	α:β ratio	yield of 4
1	Pd_2dba_3 (2 mol%)	68%	7%	10:1	22%
2*	**$P^{tBu}{}_2N^{ArCF3}{}_2$** Pd G3 (4 mol%)	68%	6%	11:1	25%
3	$Pd(OAc)_2$ (4 mol%)	60%	4%	15:1	35%
4	$[Pd(allyl)Cl]_2$ (2 mol%)	9%	1%	9:1	1%
5	**$P^{tBu}{}_2N^{ArCF3}{}_2$** Pd G3 (4 mol%)	71%	7%	10:1	21%

*No 4 mol% ligand was added
All reactions were conducted at 0.1 mmol scale
All yields were determined by ^1H NMR with 1,2,4,5-tetramethylbenzene as the internal standard

At this point, we were aiming to improve our regioselectivity and the product yield by adjusting parameters in the reaction. Subjecting additives into the reaction became an interest to us since positive contributions were observed in many Pd-catalyzed

cross-couplings.[70–74] As shown in Table 5, we examined a range of additives. In the presence of lithium triflate (LiOTf), the reaction gave a 21:1 α:β ratio and maintained the yield of the desired product (entry 2). None of the other additives generated the same improvement in the reaction. For lithium halides, both LiBr (entry 3) and LiCl (entry 4) additives were deleterious to the reactivity; and the presence of LiI (entry 5) stopped the reaction from happening. For other lithium salts, $LiBF_4$ (entry 6) showed some improvement in the regioselectivity but the amount of Suzuki product was increased; the addition of $LiNTf_2$ (entry 7) showed a reduction in desired reactivity. Lithium trifluoroacetate (LiTFA) switched the reactivity towards the Suzuki reaction and generated product **4** in 81% yield (entry 8). This can be a result of trifluoroacetate acting as a base that facilitates the Suzuki pathway. All of the triflate salts screened did not provide any positive effects on the reaction (entries 9-12), especially for AgOTf, which completely shut down any reactivity (entry 13). The boost in selectivity with lithium triflate was not intuitive to us. In literature, LiOTf additive was also noticed to enhance a Heck reaction in a few examples. Watson and co-workers realized that LiOTf can suppress the isomerization of aliphatic olefins in the Pd-catalyzed boryl-Heck reaction.[73] Leitch and others also discovered LiOTf can boost the performance of Pd catalyst in the α-arylation of vinyl ethers, suggesting that LiOTf can help with the formation of cationic Pd intermediates from Pd precatalysts.[74] In this case, we think our result could be comparable to the Leitch report, in which LiOTf may play a role in controlling the formation of cationic Pd species and enforcing the Heck reaction to go through the cationic pathway. One evidence of our reaction going through the cationic pathway is the deleterious lithium halide additives. According to Jutland, halide additives can change a cationic Pd species into a neutral Pd species; and if a Pd-catalyzed reaction is inhibited by the addition of halide salts, the reaction is likely to proceed via a cationic Pd intermediate.[70]

Table 5. Screening of additives for the coupling of 4-cyanophenyl triflate and vinylBpin



entry	additives	Yield of 3b	yield of 3b′	α:β ratio	yield of 4
1	none	68%	6%	11:1	25%
2	LiOTf	65%	3%	21:1	21%
3	LiBr	36%	4%	9:1	15%
4	LiCl	29%	3%	10:1	16%
5	LiI	0%	0%	/	0%
6	$LiBF_4$	55%	3%	18:1	37%
7	$LiNTf_2$	54%	5%	11:1	20%
8	LiTFA	11%	13%	1:1.2	81%
9	KOTf	57%	6%	10:1	20%
10	NaOTf	52%	4%	13:1	14%
11	NEt_4OTf	55%	5%	11:1	20%
12	NBu_4OTf	47%	5%	10:1	35%
13	AgOTf	0%	0%	/	0%

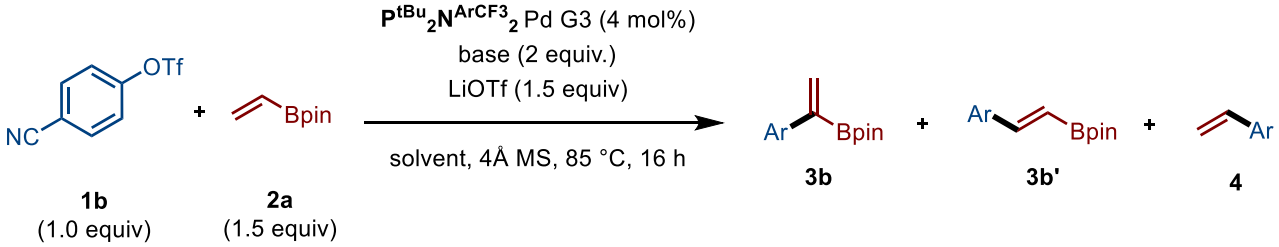
All reactions were conducted at 0.1 mmol scale

All yields were determined by ^1H NMR with 1,2,4,5-tetramethylbenzene as the internal standard

We also investigated the effect of bases and solvents in this reaction, as illustrated in Table 6. TMP was the best base in this Heck system (entry 1) consistent with our lab's recent report.[45] Triethylamine (Et_3N) yielded lower conversion to the desired product and the regioselectivity was dropped (entry 2). Inorganic bases such as cesium carbonate and cesium fluoride favored the Suzuki reaction (entries 3-4). The addition of 4Å molecular sieves was shown to have more consistent results throughout our screening, possibly because it minimized the moisture level in the solvent as water from solvent can promote the Suzuki reaction.[69] This also allowed us to evaluate the solvent effect and reduce the biases from the water. For the solvent screening, tetrahydrofuran (THF) and trifluorotoluene ($PhCF_3$) provided comparable reactivity and regioselectivity to toluene (entries 5-6). 1,2-Dichloroethane (DCE) also produced the desired product in good yield

but showed a drop in selectivity (entry 7). The Suzuki reaction was favored and no α-product was observed when polar amide solvents such as N,N-dimethylformamide (DMF) or N,N-dimethylacetamide (DMA) were used (entries 8-9). This result is consistent with the previous report in which amide solvents are favored towards the Suzuki coupling of aryl triflates.[75] Last but not least, fluorobenzene (PhF) was found to give the best yield of the desired α-product and no loss of regioselectivity compared to toluene (entry 10). At this point, we were confident that these reaction conditions give us the best results and they were applied to evaluate the substrate scope (section 2.2.3).

Table 6. Screening of bases and solvents for the coupling of 4-cyanophenyl triflate and vinylBpin



entry	base	solvent	Yield of 3b	yield of 3b′	α:β ratio	yield of 4
1	TMP	PhMe	65%	3%	21:1	21%
2	Et_3N	PhMe	55%	5%	11:1	20%
3	Cs_2CO_3	PhMe	18%	3%	6:1	55%
4	CsF	PhMe	31%	5%	6:1	57%
5	TMP	THF	57%	3%	19:1	21%
6	TMP	$PhCF_3$	65%	4%	16:1	22%
7	TMP	DCE	68%	8%	9:1	14%
8	TMP	DMF	0%	16%	/	76%
9	TMP	DMA	0%	3%	/	72%
10	TMP	PhF	75%	4%	19:1	22%

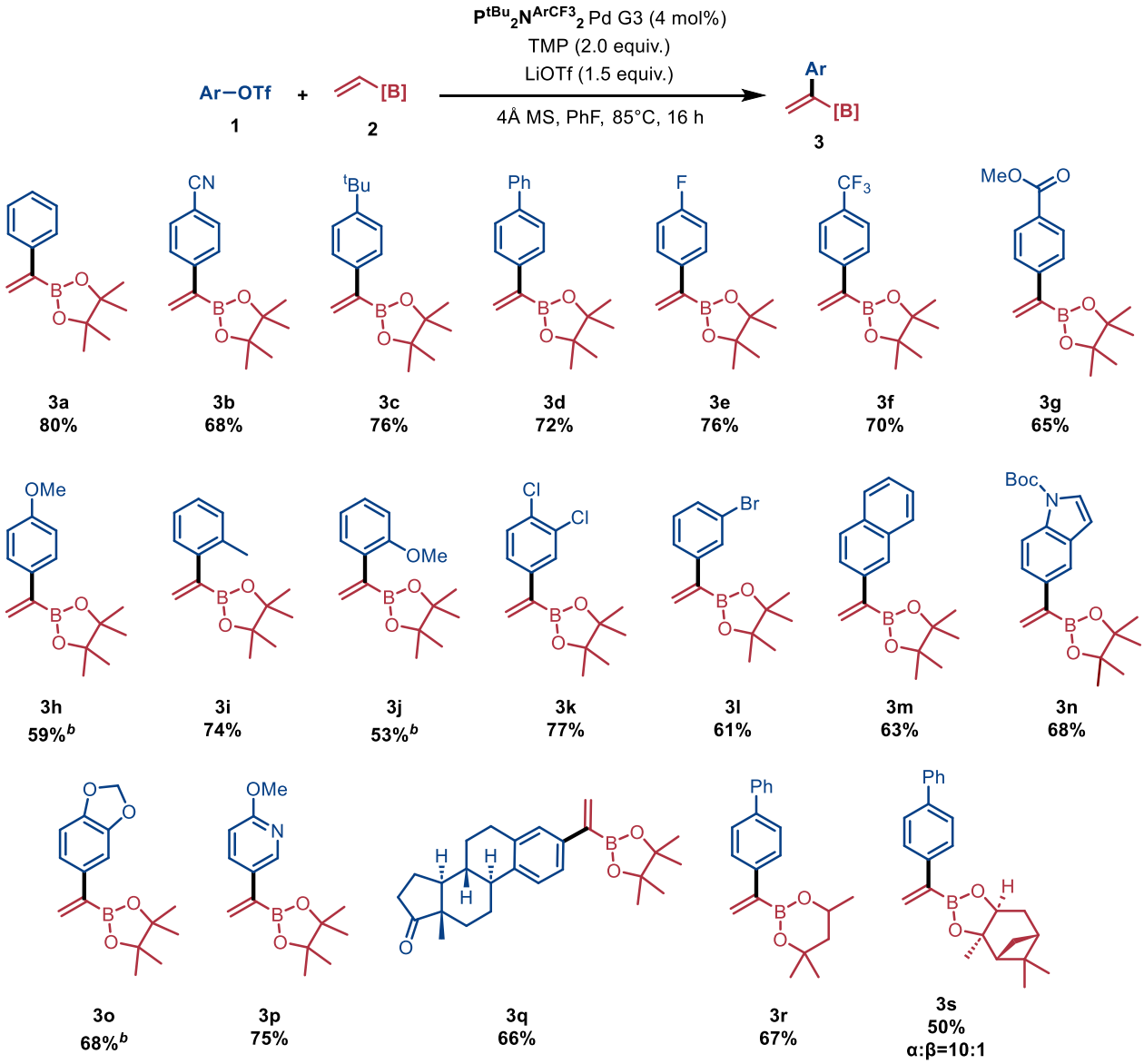
All reactions were conducted at 0.1 mmol scale
All yields were determined by ^{1}H NMR with 1,2,4,5-tetramethylbenzene as the internal standard

2.2.3 Scope of the α-selective arylation of vinylboron compounds

A range of aryl triflates was found to undergo the desired α-arylation of

vinylboronate in good yield and excellent regioselectivity (Scheme 25). Electron-withdrawing and electron-neutral aryl triflates can undergo the reaction smoothly with high yield (**3a**-**3g**). An electron-donating triflate was also able to yield the desired product (**3h**), although lower reactivity was observed and extra Pd loading was needed to improve the conversion. *Ortho*-substituents on the aromatic ring were also tolerated with no loss of regioselectivity (**3i**,**3j**). Aryl substrates with chloride (**3k**) or bromide (**3l**) substituents were well-tolerated and no reaction was observed with the other carbon—halide bond during this transformation. This would be useful for further diversification through functionalizing C—Cl and C—Br bonds. Extended aromatic system (**3m**), indole (**3n**), benzodioxole (**3o**), and methoxypyridine (**3p**) were also tolerated with good yield and excellent α-selectivity. Aryl triflate with an estrone backbone gave rise to the desired α-product smoothly (**3q**). This demonstrates the potential of our reaction to be applied in the diversification of larger molecules with multiple stereogenic centers. Vinylboronic acid hexylene glycol ester and (+)-vinylboronic acid pinanediol ester, providing **3r** and **3s** in 67% and 50% isolated yield, respectively. Other than compound **3s**, all the analysis of the crude reaction mixture revealed highly selective formation of the α-product in >20:1 ratio.

Scheme 25. Scope of Pd-catalyzed α-arylation of vinylboron compounds[a]

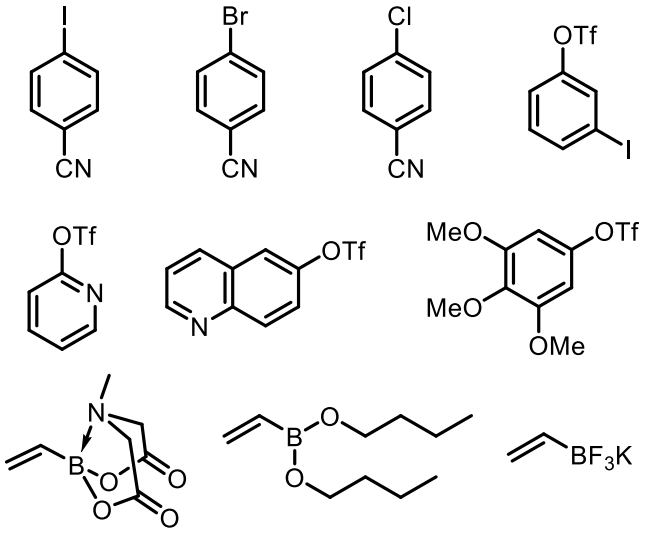


[a]General reaction conditions: aryl triflate **1** (0.2 mmol), vinylboron compound **2** (0.3 mmol), $\mathbf{P^{tBu}_2N^{ArCF3}_2}$ Pd G3 (0.008 mmol, 4 mol%), TMP (0.3 mmol), LiOTf (0.3 mmol), 4Å MS (100 mg), PhF (2 mL), 85°C, 16 h, under nitrogen atmosphere. Unless indicated, α:β ratios are >20:1 as determined by GC-FID with the crude reaction mixture. [b] 6 mol% Pd was used.

There were several aryl halides/pseudohalides or vinylboron species that failed to give the desired product or gave products that we were unable to purify (Figure 1). We

subjected aryl iodide, aryl bromide, and aryl chloride in our reaction. We found none of these aryl halides can provide any cross-coupling products. For aryl bromide and chloride, we thought the oxidative addition step could be challenging. From the substrate scope, we demonstrated two successful halide-containing substrate **3k** and **3l**, which implies that only the C—OTf bond was activated instead of the C—Br or C—Cl bond. For the failure of aryl iodides, giving that the aryl iodide oxidative addition is more facile than aryl triflate,[4] the reason is likely to be something other than a challenging oxidative addition. We selected to use an iodophenyl triflate in the reaction, presuming oxidative addition into the C—I bond is faster than into the C—OTf bond. However, we did not observe any cross-coupling products. This could imply that aryl iodide is deleterious to the Pd catalyst to proceed with productive chemistry, with the possibility of forming inactive Pd species after C—I oxidative addition and deactivating the catalyst. Further studies such as conducting stochiometric reactions may provide more clues to identify the intermediates involved. 2-pyridyl, quinoline, and trimethoxyphenyl triflate provided the desired products (as confirmed by crude GC analysis), however, these products were unstable on silica and we were unable to recover them from column chromatography. We also subjected vinylboronic acid MIDA ester to our reaction conditions, but no reactivity was observed. The dibutyl ester of vinylboronic acid and potassium vinyltrifluoroborate did not provide any Heck products, instead, they favored the Suzuki reaction and provided the corresponding styrene product exclusively. This observation aligns with the literature, where no Heck coupling of vinyl$B(OBu)_2$ or vinylBF_3K has been reported. Instead, they are often used as a source of vinyl group in Suzuki reactions.[76–78]

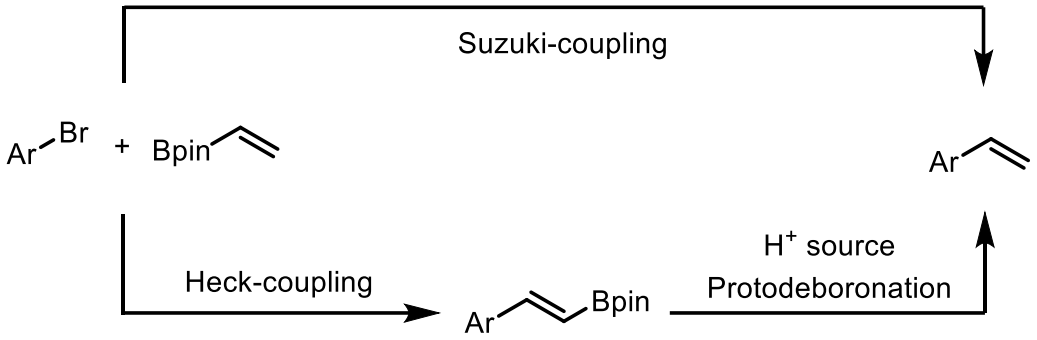
Figure 1. Unsuccessful substrates towards the α-arylation



2.2.4 The styrene product: Suzuki or protodeboronation

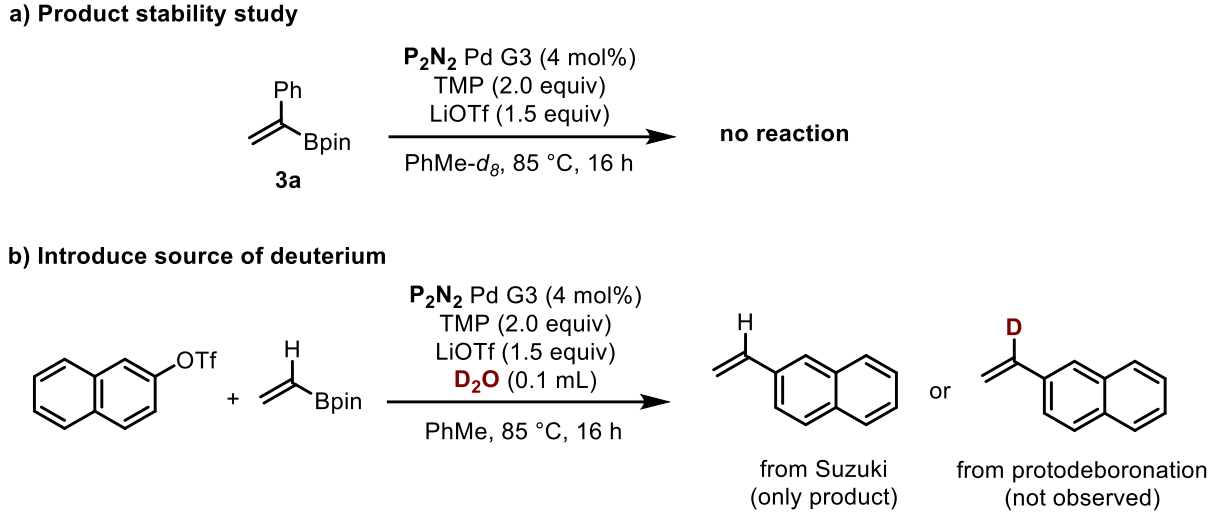
While we were assuming the styrene-type products are the result of a Suzuki coupling reaction catalyzed by the Pd catalyst, Yu and colleagues reported that styrene can also come from the protodeboronation of the alkenyl boronates.[68] The authors were studying the Heck coupling of aryl bromides and vinylBpin under Pd-catalyzed conditions. They realized that as the reaction progressed, the amount of Heck product decreased, giving rise to more styrene products. As shown in Scheme 26, a Heck+protodeboronation pathway and a Suzuki pathway were proposed by the authors to both contribute to formation of the styrene product.

Scheme 26. Styrene product from Suzuki and protodeboronation



To investigate if this potential pathway was operative in our catalytic system, we conducted two reactions. We first subjected our α-vinylboronate product **3a** to our standard conditions inside an NMR tube so we could run real-time NMR experiments to see if we had any formation of the styrene product (Scheme 27a). Over the course of 16 hours, we did not observe any formation of styrene or loss of starting material, suggesting our product is stable under our reaction conditions and no evidence of protodeboronation was found. We also deliberately introduced a source of deuterium by adding D_2O to our reaction. If the protodeboronation mechanism is active, we should be able to observe some of the deuterium-incorporated styrene in the crude mixture. However, no deuterium-incorporated product was observed at the end. Therefore, we are confident that the protodeboronation is not operative under our reaction conditions, and the styrene products are the result of Suzuki coupling.

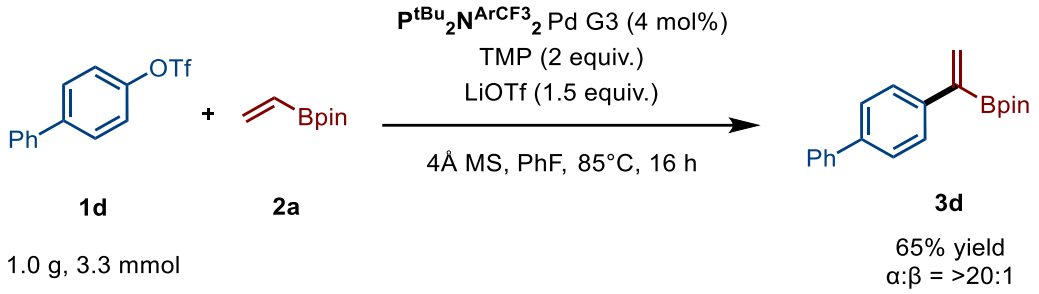
Scheme 27. Probe reactions for protodeboronation



2.2.5 Scale-up reaction and product derivatizations

With the goal of developing a practical and reliable reaction methodology, we performed a scale-up reaction at 1 mmol scale with aryl triflate **1d**. As shown in Scheme 28, we were able to isolate the desired product **3d** which is 65% yield from this scale-up reaction. Meanwhile, the regiomeric ratio is determined as 33:1 by GC-FID which is consistent with the excellent regioselectivity (>20:1) observed in most of the substrates. Compared to our substrate scope, which was conducted at 0.2 mmol scale, the gram-scale reaction did not result in any drop in yield or α-selectivity, demonstrating the robustness of this methodology in a scale-up synthesis.

Scheme 28. Scale-up synthesis (1 gram) of α-vinylboronate **3d**



1d | **2a** | **3d**

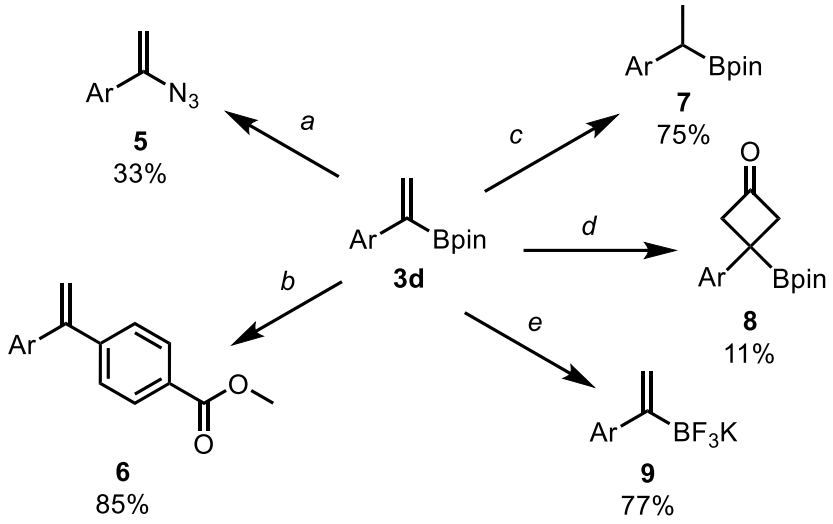
1.0 g, 3.3 mmol

65% yield
α:β = >20:1

Scale-up reaction conditions: 4-phenylphenyl triflate **1d** (1.0 g, 3.3 mmol), vinylboronic pinacol ester **2a** (0.84 mL, 5.0 mmol), $\mathbf{P^{tBu}_2N^{ArCF3}_2}$ Pd G3 (119 mg, 0.13 mmol), TMP (1.1 mL, 6.6 mmol), LiOTf (774 mg, 5.0 mmol), 4Å MS (500 mg), PhF (10 mL), 85°C, 16 h, under nitrogen atmosphere. Isolated yields are shown and the crude α:β ratios were determined GC-FID.

To showcase the utility of the α-alkenyl boron product, we decided to derivatize product **3d** into a variety of molecular scaffolds using literature conditions (Scheme 29). An α-alkenyl azide **5** can be prepared from a Cu-catalyzed reaction that converts the boronate functional group into an azide with NaN_3.[79] Suzuki-Miyaura coupling of **3d** and an aryl bromide proceeds smoothly under Pd-catalyzed conditions to give 1,1-diaryl olefin product **6** with 85% yield.[63] We also demonstrated an example of boron-retentive transformation with hydrogenation of the alkene. Under hydrogen gas, palladium on carbon (Pd/C) catalyst effectively hydrogenated **3d** to afford alkyl boron compound **7** in 75% yield.[56] The recent method from Mykhailiuk and co-workers enabled synthesis of borylated cyclobutanone **8** by a thermal [2+2] cycloaddition in 11% yield.[80] Lastly, the conversion to potassium vinyl trifluoroborate **9** was achieved with KHF_2 in 77% yield.[81]

Scheme 29. Product derivatizations with α-vinylboronate **3d**

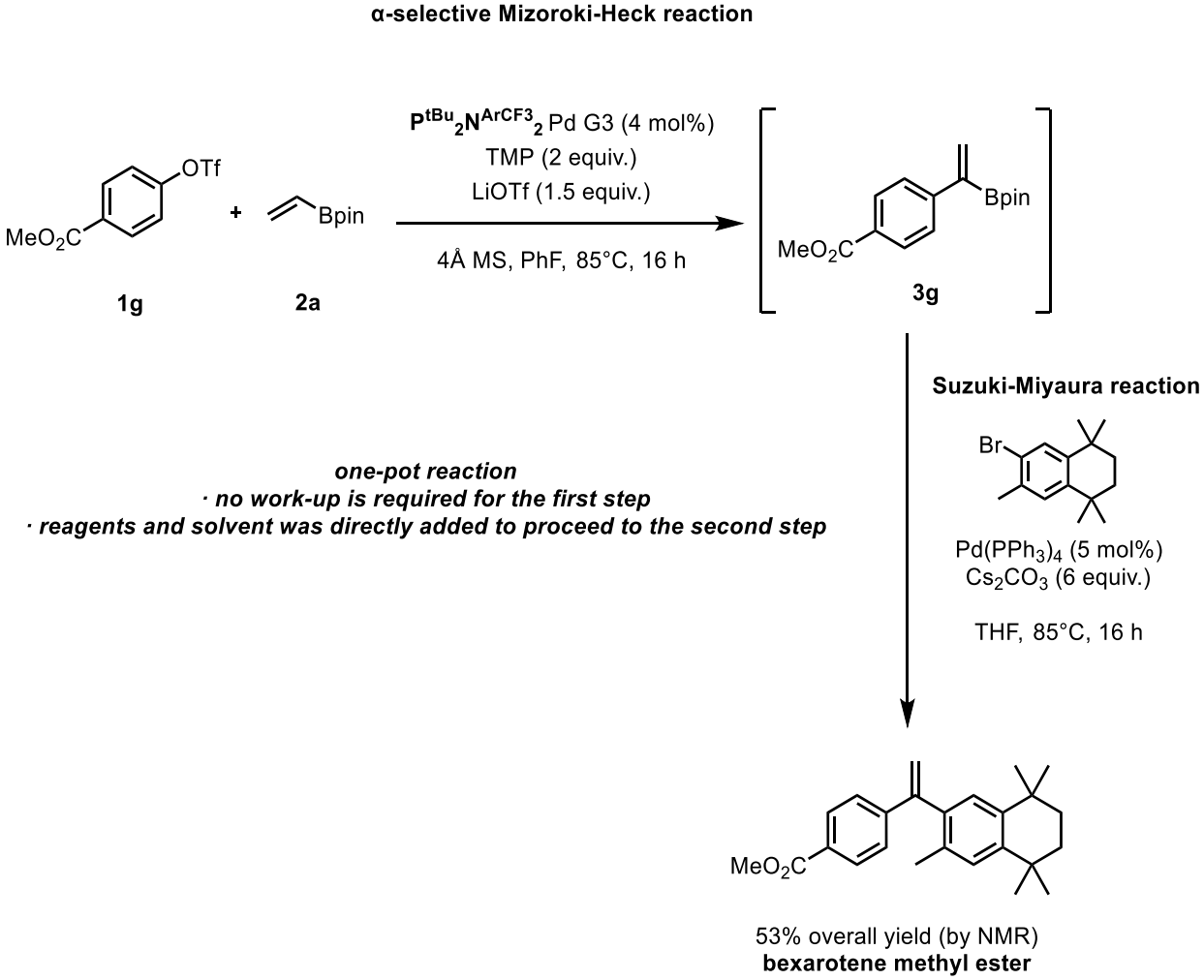


[a]**3d** (0.20 mmol), NaN_3 (0.24 mmol), $CuSO_4$ (0.12 mmol), MeOH, r.t., 6 h. [b]**3d** (0.20 mmol), methyl 4-bromobenzoate (0.20 mmol), $Pd(PPh_3)_4$ (0.04 mmol), Cs_2CO_3 (1.2 mmol), THF, 85°C, 16 h. [c]**3d** (0.20 mmol), 10% Pd/C (3 mg), H_2 balloon, MeOH, r.t., 16 h. [d]**3d** (0.20 mmol), N,N-dimethylacetamide (0.24 mmol), Tf_2O (0.28 mmol), 2,4,6-collidine (0.28 mmol), DCE, reflux, 16 h. [e]**3d** (0.20 mmol), KHF_2 (0.66 mmol), MeOH/H_2O, r.t., 3 h.

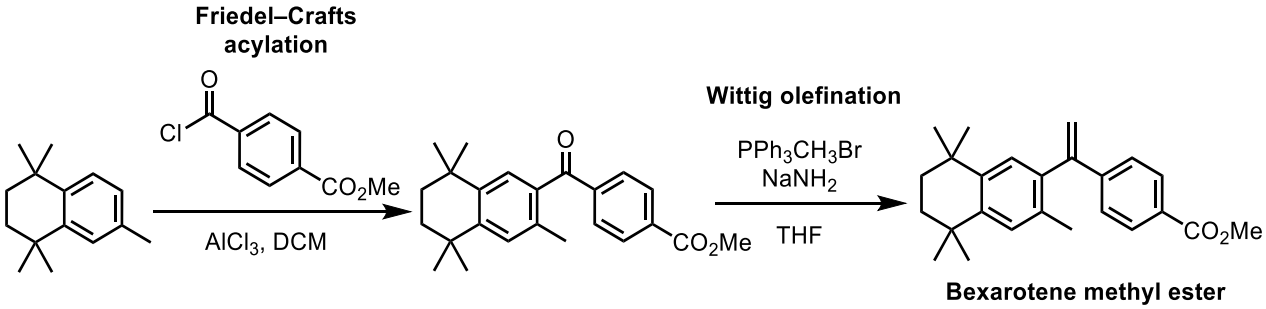
We also aim to develop a synthetic method to have rapid access to pharmaceutical-related molecules by utilizing our regioselective Heck reaction of vinylboronates. We identified bexarotene methyl ester as our target for a one-pot Heck-Suzuki reaction. Bexarotene methyl ester is an analog and also a key intermediate to bexarotene, a medication to treat cutaneous T-cell lymphoma.[82,83] Structurally, bexarotene methyl ester is a 1,1-diarylalkene, which is the target structural motif we sought to obtaining via a Heck-Suzuki process. Scheme 30 shows the optimal conditions we found to provide the best overall yield of bexarotene methyl ester. We started from methyl 4-(trifluoromethylsulfonyloxy)benzoate (**1g**), which undergoes the Heck reaction under our standard conditions to generate the alkenyl boron product **3g**. No work-up or isolation of this intermediate was needed and we then subjected the subsequent reagents

to the “pot”. We selected commercially available aryl bromide (6-bromo-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydronaphthalene) to participate in the second coupling reaction along with $Pd(PPh_3)_4$ and cesium carbonate base. Noteworthy, a portion of THF solvent was also added to the “pot” to make a 1:1 PhF:THF solvent system in the second step, which was shown to have a better conversion of intermediate **3g** into the desired product. Overall, we were able to obtain bexarotene methyl ester in 53% NMR yield via this one-pot Heck-Suzuki process. In the literature, the synthetic route of bexarotene methyl ester consists of two non-catalytic steps starting from a tetrahydropentamethylnaphthyl motif and a methyl benzoate fragment, as shown in Scheme 31.[82] A ketone intermediate has to be formed first through Friedel-Crafts acylation before being subjected to Wittig olefination conditions to obtain the desired 1,1-diarylolefin product. In comparison, our "one-pot" Pd-catalyzed condition offers a more direct route without the need to isolate any intermediates, and provides a milder reaction condition without the use of a strong base.

Scheme 30. One-pot synthesis of bexarotene methyl ester



Scheme 31. Literature synthetic route of bexarotene methyl ester



2.2.6 Conclusion and future directions

To sum up, we developed an efficient method of synthesizing α-styrenyl boronates via a highly regioselective Mizoroki-Heck reaction. The catalyst system that consists of a Pd salt and a unique 1,5-diaza-3,7-diphosphacyclooctane ligand was found to enable this regioselective reaction. Lithium triflate additive was identified to boost the regioselectivity. A range of aryl triflates were able to provide the desired products in good yield and over 20:1 regiomeric ratio. This reaction is presumed to undergo the cationic Heck mechanism, in which a cationic palladium intermediate is required to enable the Heck reactivity. The addition of coordinating anions which were found to suppress the reaction, provides a piece of evidence for the operative cationic mechanism. The practical aspects of this reaction were also demonstrated by a successful scaling up experiment and a one-pot Heck-Suzuki reaction.

As mentioned earlier, even though the Heck reaction is one of the fundamental and most studied cross-coupling reactions, it is still underutilized in the synthesis of useful molecules such as drug molecules. We believe one of the reasons for this is that the reactivity and selectivity of a Heck reaction is dependent on the substrates and may not be generally applicable to many desired structures. We hope our work on the Pd/P_2N_2 system will advance this field by demonstrating a robust and highly selective Heck reaction to synthesize α-styrenyl boronates. Future directions extended from this project would be exploring more olefin coupling partners or employing nickel catalysis to involve a diverse range of electrophiles in the highly selective Heck reaction as an inspiration from Jamison's work.[35] In addition, further studies in developing new reaction methodologies with the 1,5-diaza-3,7-diphosphacyclooctane ligands and understanding their roles in cross-coupling reactions would be a reasonable future work from our lab or from the field, as they are underexplored in organic transformations. We

are optimistic about the potential of these P_2N_2 ligands in diverse metal-catalyzed cross-coupling reactions, and we anticipate that this ligand class will become a valuable and practical resource in the toolbox of synthetic chemists.

2.3 Experimental section

2.3.1 General experiment details

Unless otherwise indicated, reactions were conducted under an atmosphere of nitrogen in 8 mL screw-capped vials that were oven dried (120 °C) or flame dried and shipped into a glovebox. Column chromatography was either performed manually using Silicycle F60 40–63 μm silica gel or using boric acid impregnated silica for purifying boron-containing compounds. Analytical thin-layer chromatography (TLC) was conducted with aluminum-backed EMD Millipore Silica Gel 60 F254 pre-coated plates. Visualization of developed plates was performed under UV light (254 nm). For certain purifications, potassium permanganate ($KMnO_4$) stains were used to better visualize the compounds on the TLC plates.

2.3.2 Instrumentation

^{1}H NMR, ^{13}C NMR, ^{11}B NMR, and ^{19}F NMR were recorded on a Bruker AVANCEII 300 MHz spectrometer, a Bruker AVANCEII 400 MHz spectrometer, or a Bruker AVANCEIII 500 MHz spectrometer. ^{1}H NMR spectra were internally referenced to the residual solvent signal (e.g., $CDCl_3$ = 7.26 ppm). ^{13}C NMR spectra were internally referenced to the residual solvent signal (e.g., $CDCl_3$ = 77.15 ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. NMR yields for optimization studies were obtained by ^{1}H NMR analysis of the crude reaction mixture using 1,2,4,5-tetramethylbenzene as an internal standard. For alkenyl boron compounds, only the ^{1}H and ^{13}C NMR spectral data were used to compare with the literature values as the ^{11}B data were not always reported.

2.3.3 Materials

Organic solvents were purified by rigorous degassing with nitrogen before passing through a PureSolv solvent purification system. Low water content was confirmed by Karl Fischer titration (<25 ppm for all solvents). Unless otherwise noted, reagents were used as received. Pd_2dba_3 was purchased from Sigma Aldrich or Oakwood Chemical and used without further purification. Phenylphosphine was obtained as a 10% wt. solution in hexanes from Sigma Aldrich. Cyclohexylphosphine and tert-butylphosphine were generously donated from Cytec-Solvay as neat liquids. Primary phosphines were stored and used in the glovebox to avoid any reaction with oxygen. The P_2N_2 ligands and Pd G3 pre-catalysts used were prepared previously by our lab, but they can also be prepared from a literature procedure.[84] Commercial ligands were purchased from Sigma Aldrich, Combi-Blocks, Fisher Scientific, or Strem Chemicals. Vinylboronic acid pinacol ester was obtained from Oakwood Chemicals and Combi-Blocks. 2,2,6,6-Tetramethylpiperidine (TMP) was obtained from Oakwood Chemicals and Combi-Blocks. Aryl triflates were synthesized following a general procedure (Section 2.3.5). Other vinylboronates were synthesized following a general procedure (Section 2.3.5). Unless otherwise noted, all other commercially available starting materials were obtained from Sigma-Aldrich, TCI America, Fisher Scientific, Acros Organics, Alfa Aesar, Combi-Blocks, Aaron Chemicals, or Oakwood Chemicals and used as received. 4Å molecular sieve beads were obtained from Aldrich. Molecular sieves were properly dried on aluminum foils under vacuum and 280 °C for 3 hours inside a vacuum oven and stored inside the glovebox. Ground molecular sieves were prepared by crushing beads into powders using a mortar and a pestle in the glovebox.

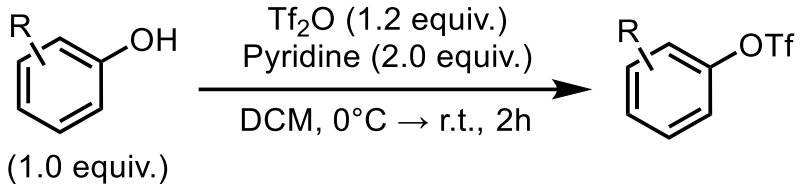
2.3.4 Boric acid impregnated silica

It is known that some organoboronates are prone to be over-absorbed and decomposed on commercial silica gel, resulting in lower isolated yields or even loss of products during column chromatography.[85,86] The emergence of boric acid impregnated silica has been used to reduce this decomposition during isolation. This is shown to be effective in isolating organoboron compounds with several examples.[73,85,87] In our practice, we found that the use of boron-impregnated silica results in more consistent isolated yields with our vinylboron compounds compared to untreated silica gel.

The boric acid impregnated silica was prepared by following a procedure adapted from the literature.[85] A 1L round bottom flask was charged with Silicycle F60 40−63 μm silica gel (300 mL), boric acid (28 g), and ethanol (550 mL) under air. The suspension was constantly shaken by hand over the period of 2 hours. The solvent was then removed by vacuum filtration through fine glass frit and the residue was washed with ethanol (3 x 200 mL). The impregnated silica was then transferred into a proper-size glass container and dried in the oven (120 ℃) overnight before use in column chromatography.

2.3.5 General procedures

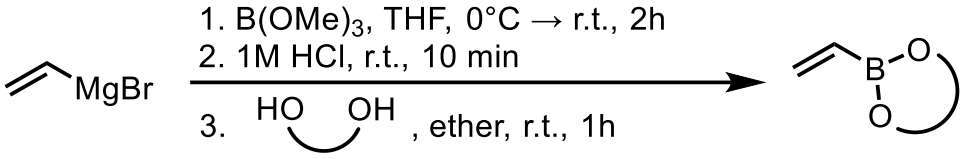
General procedure A: Synthesis of aryl triflates



Aryl triflates were synthesized following the literature procedure with a few

modifications.[88] The phenol derivative (1.0 equiv.) was weighed and added to an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar. DCM (10 mL) and pyridine (2.0 equiv.) were added to the flask and stirred in an ice bath (0 °C) for about 10 minutes. Trifluoromethanesulfonic anhydride (1.2 equiv.) was then added to the stirring solution dropwise. After complete addition, the reaction was allowed to warm up to room temperature and then allowed to stir for 2 hours. The reaction was then quenched with 1M HCl and stirred for another 10 minutes. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted three times with DCM (3 × 10 mL) in a separatory funnel and the organic layers were combined. The combined organic layer was dried with $MgSO_4$ and vacuum filtered. The filtrate was collected and the solvent was removed *in vacuo*. The residue was purified by column chromatography (Et_2O/hexanes) to obtain pure aryl triflate.

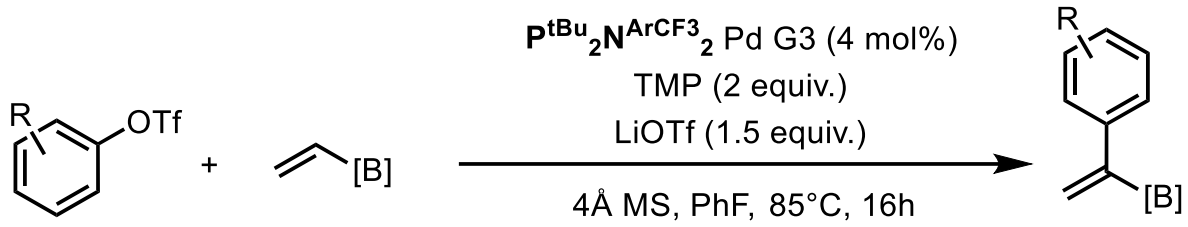
General procedure B: Synthesis of vinylboronates



Vinylboronates were synthesized following the literature procedure.[66] In a 100 mL round-bottomed flask, vinylmagnesium bromide 1.0 M solution in THF (5.0 mL, 5.0 mmol, 1.0 equiv.) was added dropwise to a stirred solution of trimethyl borate (0.94 mL, 9.0 mmol, 1.8 equiv.) in anhydrous THF (5 mL) at -78°C under nitrogen. The reaction was allowed to warm up to room temperature after stirring for 1 hour and kept stirring for another 1 hour. 1M HCl solution (10 mL) was then added to the reaction mixture and stirred for 10 minutes. A solution of diol (5.0 mmol, 1.0 equiv.) in ether (10 mL) was added

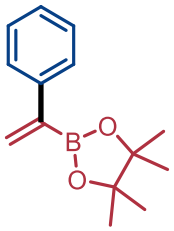
to the reaction mixture and stirred for 1 hour. After the reaction was completed, the organic phase was separated from the reaction mixture and washed with saturated aq. $NaHCO_3$ (10 mL × 2) and distilled water (10 mL × 2). The combined organic layer was dried with $MgSO_4$ and vacuum filtered. The filtrate was collected and the solvent was removed *in vacuo* to yield the pure vinylboronate as a colorless liquid.

General procedure C: Synthesis of *α*-vinylboronates from aryl triflates and vinylboronates



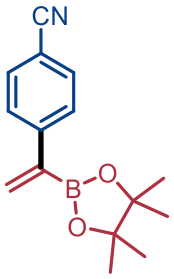
An oven-dried 8 mL screw-capped vial charged with a magnetic stirring bar was shipped into a nitrogen-filled glovebox. $\mathbf{P^{tBu}_2N^{ArCF3}_2}$ Pd G3 (7.4 mg, 0.008 mol), LiOTf (46.8 mg, 0.3 mol), and ground 4Å molecular sieve (100 mg) were weighed and added to the vial. Phenyl triflate (0.2 mol) was dissolved in PhF (2 mL) and added to the reaction vial. Vinylboronate (0.3 mol) and 2,2,6,6-tetramethylpiperidine (68.1 μL, 0.4 mol) were added to the stirring solution. The reaction vial was shipped out from the glovebox and put on an oil bath pre-set at 85°C for an overnight reaction (16 h). The reaction mixture was then diluted with Et_2O and filtered through a plug of Celite to remove any insoluble solid residues. The solvent was removed under vacuum and the crude product was purified by flash column chromatography with boric acid impregnated silica.

2.3.6 Characterization data for α-vinylboronates and derivatized products



3a

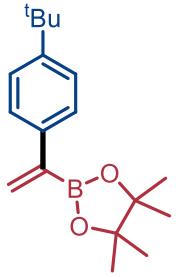
4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (3a) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3a** as a colorless liquid (36.5 mg, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.50-7.47 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.22 (m, 1H), 6.09-6.05 (m, 2H), 1.33 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 141.5, 131.0, 128.3, 127.3, 127.1, 83.9, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.5. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[64]



3b

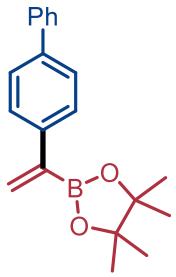
4,4,5,5-tetramethyl-2-(1-(4-cyanophenyl)vinyl)-1,3,2-dioxaborolane (3b) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% acetone in hexanes to afford **3b** as a white solid (34.6 mg, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.61-7.55

(m, 4H), 6.21 (d, J = 2.6 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 1.32 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 146.2, 134.0, 132.1, 128.0, 119.3, 110.6, 84.3, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.0. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. **HRMS (EI-Magn. Sector)** *m*/*z*: Calcd for $C_{15}H_{18}O_2NB$ $[M]^+$ 255.1409; Found: 255.1420.



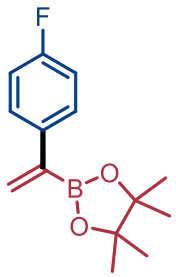
3c

4,4,5,5-tetramethyl-2-(1-(4-tert-butylphenyl)vinyl)-1,3,2-dioxaborolane (3c) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3c** as a colorless liquid (43.7 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.48-7.44 (m, 2H), 7.38-7.34 (m, 2H), 6.09 (d, J = 2.9 Hz, 1H), 6.04 (d, J = 3.0 Hz, 1H), 1.34 (s, 12H), 1.33 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 150.0, 138.5, 130.3, 126.9, 125.3, 83.8, 34.6, 31.5, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.6. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[63]



3d

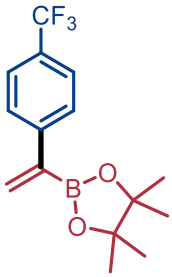
4,4,5,5-tetramethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborolane (3d) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3d** as a white solid (43.5 mg, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.62-7.59 (m, 2H), 7.57 (s, 4H), 7.46-7.41 (m, 2H), 7.36-7.31 (m, 1H), 6.15 (d, *J* = 2.5 Hz, 1H), 6.10 (d, *J* = 2.7 Hz, 1H), 1.35 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 141.2, 140.5, 140.0, 131.1, 128.8, 127.7, 127.2, 127.1, 127.1, 84.0, 25.0. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.4. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[89]



3e

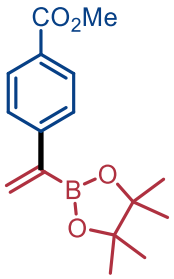
4,4,5,5-tetramethyl-2-(1-(4-fluorophenyl)vinyl)-1,3,2-dioxaborolane (3e) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3e** as a colorless liquid (37.7 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.48-7.43

(m, 2H), 7.03-6.97 (m, 2H), 6.05-6.03 (m, 2H), 1.32 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 162.4 (d, *J* = 245.5 Hz), 137.5 (d, *J* = 3.1 Hz), 130.9 (d, *J* = 1.3 Hz), 128.9 (d, *J* = 7.9 Hz), 115.2, 115.0, 84.0, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.4. **^{19}F NMR** (283 MHz, $CDCl_3$): δ (ppm) = -116.1. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[64]



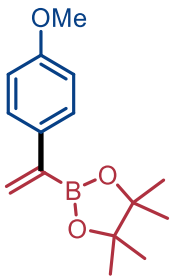
3f

4,4,5,5-tetramethyl-2-(1-(4-trifluoromethylphenyl)vinyl)-1,3,2-dioxaborolane (3f) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3f** as a colorless liquid (41.6 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.57 (s, 4H), 6.17 (d, *J* = 2.7 Hz, 1H), 6.13 (d, *J* = 2.5 Hz, 1H), 1.33 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 145.2, 133.1, 128.9, 127.6, 125.2 (q, *J* = 3.7 Hz), 123.2, 84.2, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.2. **^{19}F NMR** (283 MHz, $CDCl_3$): δ (ppm) = -62.4. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[89]



3g

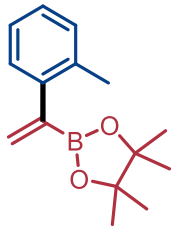
methyl 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzoate (3g) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 5% Et_2O in hexanes to afford **3g** as a white solid (41.6 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.00-7.97 (m, 2H), 7.56-7.52 (m, 2H), 6.18-6.13 (m, 2H), 3.90 (s, 3H), 1.33 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 167.2, 146.2, 132.9, 129.7, 128.6, 127.3, 84.1, 52.1, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.0. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[64]



3h

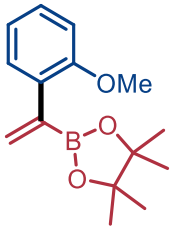
4,4,5,5-tetramethyl-2-(1-(4-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3h) was prepared according to **general procedure C** with 6 mol% of Pd. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 5% Et_2O in hexanes to afford **3h** as a colorless liquid (30.5 mg, 59%). **^{1}H NMR** (400

MHz, $CDCl_3$): δ (ppm) = 7.47-7.43 (m, 2H), 6.88-6.84 (m, 2H), 6.01 (d, *J* = 2.7 Hz, 1H), 5.96 (d, *J* = 2.8 Hz, 1H), 3.80 (s, 3H), 1.32 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 159.0, 134.1, 129.1, 128.4, 113.7, 83.9, 55.4, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.4. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[64]



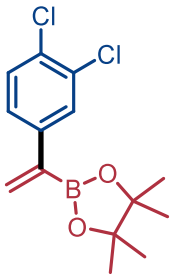
3i

4,4,5,5-tetramethyl-2-(1-(o-tolyl)vinyl)-1,3,2-dioxaborolane (3i) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3i** as a colorless liquid (30.5 mg, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.18-7.14 (m, 3H), 7.12-7.08 (m, 1H), 6.17 (d, *J* = 3.6 Hz, 1H), 5.80 (d, *J* = 3.5 Hz, 1H), 2.28 (s, 3H), 1.30 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 142.8, 135.1, 133.1, 129.8, 128.5, 127.0, 125.9, 83.9, 24.9, 20.4. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.0. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[64]



3j

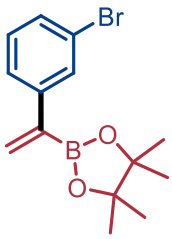
4,4,5,5-tetramethyl-2-(1-(2-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3j) was prepared according to **general procedure C** with 6 mol% of Pd. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 5% Et_2O in hexanes to afford **3j** as a colorless liquid (27.6 mg, 53%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.26-7.21 (m, 2H), 6.95-6.91 (m, 1H), 6.86-6.83 (m, 1H), 5.91 (d, *J* = 3.3 Hz, 1H), 5.87 (d, *J* = 3.2 Hz, 1H), 3.80 (s, 3H), 1.31 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 156.4, 132.0, 129.1, 128.6, 128.5, 121.1, 110.3, 83.6, 55.3, 24.8. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.3. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[64]



3k

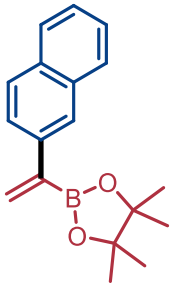
4,4,5,5-tetramethyl-2-(1-(3,4-dichlorophenyl)vinyl)-1,3,2-dioxaborolane (3k) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes

to afford **3k** as a colorless liquid (46.0 mg, 77%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.57-7.56 (m, 1H), 7.38-7.36 (m, 1H), 7.33-7.30 (m, 1H), 6.12 (d, *J* = 2.6 Hz, 1H), 6.08 (d, *J* = 2.4 Hz, 1H), 1.32 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 141.6, 132.5, 132.2, 131.0, 130.1, 129.2, 126.8, 84.2, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 29.8. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[63]



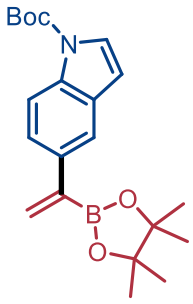
3l

4,4,5,5-tetramethyl-2-(1-(3-bromophenyl)vinyl)-1,3,2-dioxaborolane (3l) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3l** as a colorless liquid (38.0 mg, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.62-7.60 (m, 1H), 7.42-7.35 (m, 2H), 7.21-7.16 (m, 1H), 6.11-6.07 (m, 2H), 1.32 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 143.7, 132.3, 130.2, 130.0, 129.8, 126.1, 122.5, 84.1, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.1. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[63]



3m

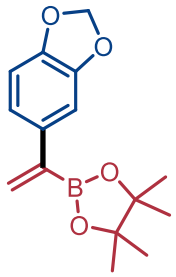
4,4,5,5-tetramethyl-2-(1-(naphthalen-2-yl)vinyl)-1,3,2-dioxaborolane (3m) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3m** as a colorless liquid (35.5 mg, 63%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.96-7.94 (m, 1H), 7.85-7.77 (m, 3H), 7.65-7.61 (m, 1H), 7.48-7.70 (m, 2H), 6.21 (d, J = 2.4 Hz, 1H), 6.15 (d, J = 2.8 Hz, 1H), 1.36 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 139.0, 133.7, 132.8, 131.3, 128.4, 127.7, 127.6, 126.3, 125.9, 125.7, 84.0, 25.0. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.4. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[63]



3n

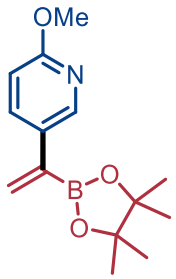
tert-butyl 5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indole-1-carboxylate (3n) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography

with 10% EtOAc in hexanes to afford **3n** as a white solid (50.4 mg, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.06 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 1.3 Hz, 1H), 7.57 (d, *J* = 3.5 Hz, 1H), 7.45 (dd, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H), 6.57 (d, *J* = 3.7 Hz, 1H), 6.11 (d, *J* = 2.9 Hz, 1H), 6.06 (d, J = 2.9 Hz, 1H), 1.68 (s, 9H), 1.35 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 149.9, 136.3, 134.5, 130.8, 130.2, 126.1, 123.8, 119.7, 114.9, 107.8, 83.9, 83.6, 28.3, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 30.2. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[90]



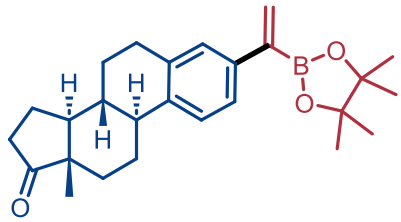
3o

4,4,5,5-tetramethyl-2-(1-(benzo[d][1,3]dioxol-5-yl)vinyl)-1,3,2-dioxaborolane (3o) was prepared according to **general procedure C** with 6 mol% of Pd. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 5% Et_2O in hexanes to afford **3o** as a colorless liquid (37.5 mg, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.02-6.98 (m, 2H), 6.79-6.76 (m, 1H), 5.99 (d, *J* = 2.6 Hz, 1H), 5.97 (d, *J* = 2.6 Hz, 1H), 5.94 (s, 2H), 1.32 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 147.6, 146.9, 135.8, 129.7, 121.0, 108.2, 107.8, 101.0, 83.9, 24.9. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[89]



3p

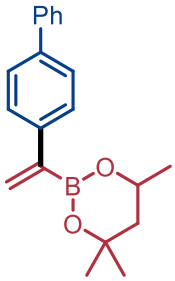
2-methoxy-5-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]pyridine (3p) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was>20:1. The product was purified by column chromatography with 10% EtOAc in hexanes to afford **3p** as a colorless liquid (39.0 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.34-8.32 (m, 1H), 7.72-7.69 (m, 1H), 6.71-6.68 (m, 1H), 6.05-6.02 (m, 2H), 3.93 (s, 3H), 1.31 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 163.4, 145.6, 137.4, 130.4, 130.3, 110.4, 84.1, 53.5, 24.9. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation.



3q

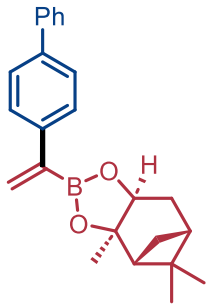
(8R,9S,13S,14S)-13-methyl-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (3q) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% acetone in hexanes to afford **3q** as a white solid (54.0 mg, 66%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm)

= 7.26-7.24 (m, 2H), 7.19-7.17 (m, 1H), 6.03 (d, *J* = 3.0 Hz, 1H), 6.00 (d, *J* = 3.0 Hz, 1H), 2.95-2.89 (m, 2H), 2.55-2.46 (m, 1H), 2.45-2.39 (m, 1H), 2.34-2.25 (m, 1H), 2.19-2.11 (m, 1H), 2.10-1.91 (m, 4H), 1.68-1.40 (m, 7H), 1.31 (s, 12H), 0.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 139.2, 138.7, 136.3, 130.4, 127.8, 125.3, 125.0, 83.9, 77.5, 77.1, 76.8, 50.7, 48.1, 44.5, 38.3, 36.0, 31.7, 29.6, 26.7, 25.8, 24.9, 24.9, 21.7, 14.0. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation. The spectral data are consistent with literature.[89]



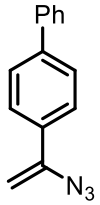
3r

4,4,6-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborinane (3r) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was >20:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3r** as a colorless liquid (40.9 mg, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.65-7.62 (m, 2H), 7.56 (s, 4H), 7.48-7.42 (m, 2H), 7.37-7.32 (m, 1H), 6.05 (d, *J* = 3.4 Hz, 1H), 5.99 (d, *J* = 3.3 Hz, 1H), 4.38-4.29 (m, 1H), 1.89-1.84 (m, 1H), 1.65-1.56 (m, 1H), 1.38 (s, 6H), 1.36-1.33 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 141.8, 141.3, 139.4, 129.0, 128.8, 128.1, 127.1, 127.1, 126.8, 71.4, 65.3, 46.0, 31.4, 28.3, 23.3. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 26.5. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation.



3s

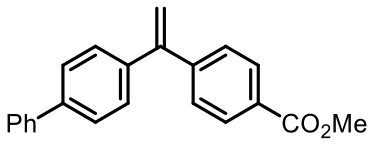
(3aS,7aR)-3a,5,5-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (3s) was prepared according to **general procedure C**. The crude α:β ratio as assessed by GC-FID was 10:1. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **3s** as a white solid (36.2 mg, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.63-7.56 (m, 6H), 7.47-7.42 (m, 2H), 7.37-7.32 (m, 1H), 6.17 (d, *J* = 2.9 Hz, 1H), 6.13 (d, *J* = 2.9 Hz, 1H), 4.44 (dd, *J* = 8.9, 1.9 Hz, 1H), 2.46-2.37 (m, 1H), 2.33-2.25 (m, 1H), 2.18-2.14 (m, 1H), 2.02-1.95 (m, 2H), 1.50 (s, 3H), 1.33 (s, 3H), 1.29 (d, *J* = 11.0 Hz, 1H), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 141.2, 140.6, 140.0, 131.1, 128.8, 127.7, 127.2, 127.1, 127.1, 86.4, 78.4, 51.5, 39.7, 38.3, 35.7, 28.3, 27.2, 26.7, 24.2. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 29.4. Note: The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation.



5

4-(1-azidovinyl)biphenyl (5) was prepared according to the literature.[63] In an oven-dried 8 mL screw-capped vial charged with a magnetic stirring bar, α-vinylboronate **3d** (61.2

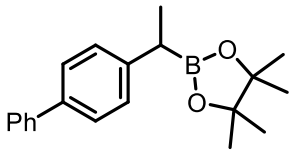
mg, 0.2 mol), NaN_3 (19.6 mg, 0.3 mol), and $CuSO_4$ (19.2 mg, 0.12 mol) were weighed and added to the vial. MeOH (1 mL) was added to the vial. The reaction was allowed to stir under air at room temperature for 16 h. The reaction mixture was then diluted with Et_2O and filtered through a plug of Celite to remove any insoluble solid residues. After the removal of solvent *in vacuo*, the product was purified by column chromatography with 1% Et_2O in hexanes to afford **5** as a white solid (14.5 mg, 33%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.66-7.57 (m, 6H), 7.48-7.42 (m, 2H), 7.39-7.34 (m, 1H), 5.49 (d, *J* = 2.4 Hz, 1H), 4.99 (d, *J* = 2.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 144.9, 142.0, 140.5, 133.3, 129.0, 127.8, 127.3, 127.2, 126.1, 98.0. The spectral data are consistent with literature.[91]



6

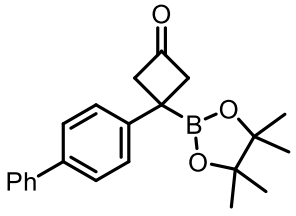
methyl 4-(1-([1,1'-biphenyl]-4-yl)vinyl)benzoate (6) was prepared according to the literature.[63] In an oven-dried 8 mL screw-capped vial charged with a magnetic stirring bar, α-vinylboronate **3d** (61.2 mg, 0.2 mol), methyl 4-bromobenzoate (43.0 mg, 0.2 mol), $Pd(PPh_3)_4$ (11.0 mg, 0.01 mol), and Cs_2CO_3 (391 mg, 1.2 mol) were weighed and added to the vial. THF (1 mL) was added to the vial. The reaction was allowed to reflux (at 85℃) for an overnight reaction (16 h). The reaction mixture was then diluted with Et_2O and filtered through a plug of Celite to remove any insoluble solid residues. After the removal of solvent *in vacuo*, the product was purified by column chromatography with 5% Et_2O in hexanes to afford **5** as a white solid (54.0 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.04-8.01 (m, 2H), 7.64-7.56 (m, 4H), 7.48-7.43 (m, 4H), 7.41-7.34 (m, 3H), 5.62 (m, 1H), 5.56 (m, 1H), 3.94 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 167.1, 149.0, 146.2, 141.0,

140.7, 139.8, 129.7, 129.5, 129.0, 128.7, 128.5, 127.6, 127.2, 127.2, 116.0, 52.3.



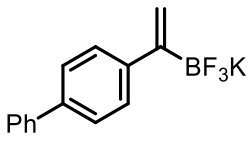
7

2-(1-([1,1'-biphenyl]-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7) was prepared according to the literature.[56] In an oven-dried 8 mL screw-capped vial charged with a magnetic stirring bar, α-vinylboronate **3d** (61.2 mg, 0.2 mol), 10% Pd/C (3.0 mg) were weighed and added. The vial was three-fold evacuated and backfilled with H_2 from a balloon. Dry THF (1 mL) was then added to the reaction. The reaction was allowed to stir at room temperature overnight (16 h). After the reaction, the reaction was filtered through a plug of Celite to remote insoluble residues. The solvent was then removed *in vacuo* and the product was purified by column chromatography with 0→5% Et_2O in hexanes to afford **5** as a white solid (46.0 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.61-7.56 (m, 2H), 7.53-7.49 (m, 2H), 7.44-7.39 (m, 2H), 7.33-7.27 (m, 3H), 2.48 (q, *J* = 7.5 Hz, 1H), 1.37 (d, *J* = 7.5 Hz ,3H), 1.23 (s, 6H), 1.22 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 144.3, 141.4, 138.1, 128.8, 128.3, 127.2, 127.1, 126.9, 83.5, 24.8, 24.7, 17.2. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 33.2. The spectral data are consistent with literature.[92]



8

3-([1,1'-biphenyl]-4-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutanone (8) was prepared according to the literature.[80] In an oven-dried 10 mL round-bottom flask charged with a magnetic stirring bar, N,N-dimethylacetamide (22 μL, 0.24 mmol, 1.2 equiv.) was dissolved in dichloroethane (1 mL). The flask was then allowed to cool down to -15 ℃. Triflic anhydride (47 μL, 0.28 mmol, 1.4 equiv.) was added to the stirring reaction mixture. After 15 minutes stirring, 2,4,6-collidine (33.9 mg, 0.28 mmol, 1.4 equiv.) and **3d** (61.2 mg, 0.2 mmol, 1 equiv.) was added to the flask while stirring. The reaction was then brought up to heat and reflux for 16 h. The solvent was then removed under reduced pressure and sat. $NaHCO_3$ solution (1 mL) and hexane (1 mL) were added to the flask and stirred for 1 h. The organic phase was washed with 1M HCl solution and water and with $MgSO_4$ and vacuum filtered. The filtrate was collected and the solvent was removed *in vacuo*. The product was purified by column chromatography with 1% Et_2O in hexanes to afford **8** as a white solid (8.1 mg, 11%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.62-7.55 (m, 4H), 7.47-7.30 (m, 5H), 3.64-3.57 (m, 2H), 3.43-3.32 (m, 2H), 1.20 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ (ppm) = 206.5, 144.7, 140.9, 138.6, 128.9, 127.3, 127.3, 127.2, 127.1, 84.5, 56.4, 24.6. **^{11}B NMR** (96 MHz, $CDCl_3$): δ (ppm) = 33.1. The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation.



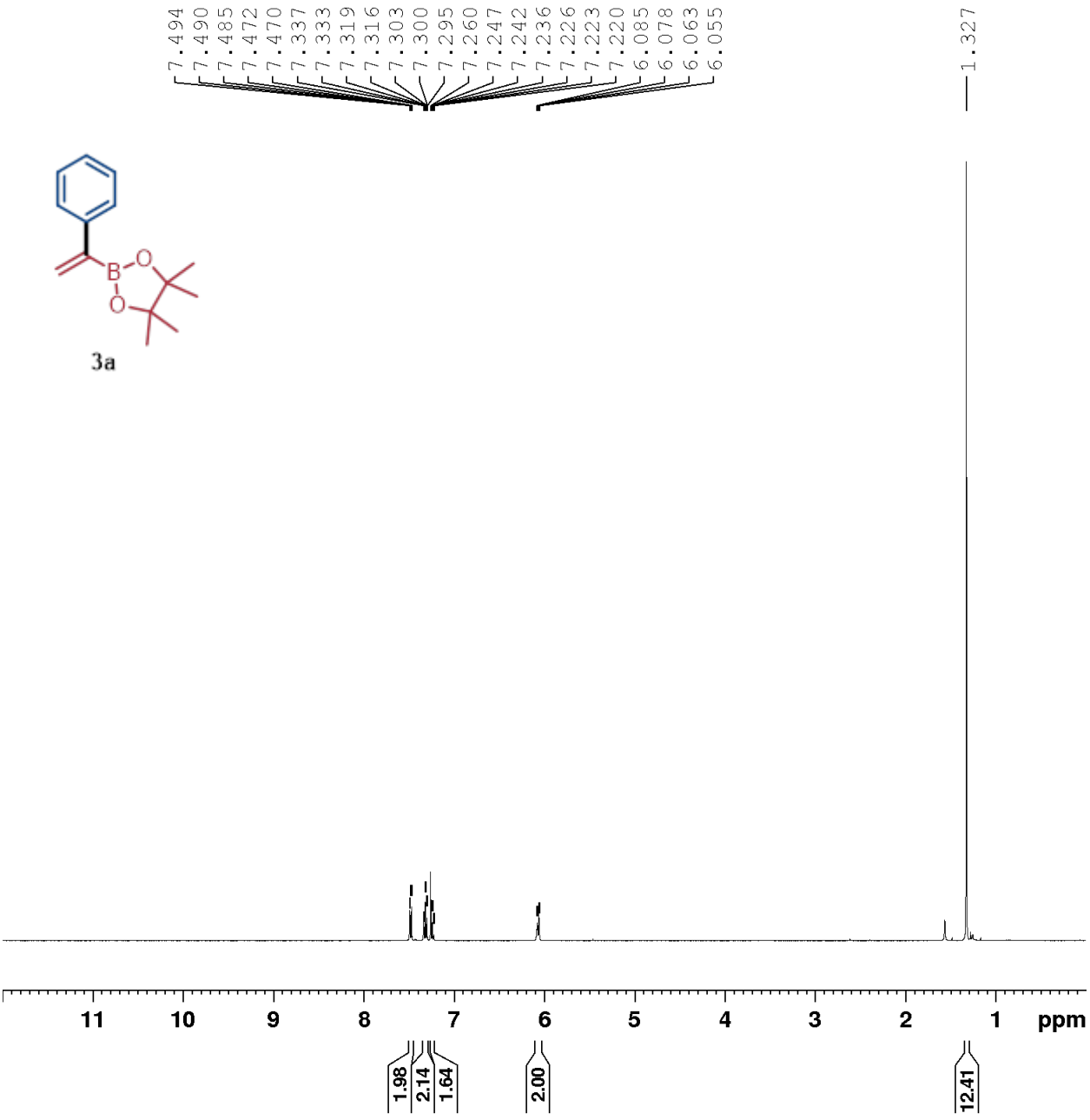
9

Potassium (1-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate (9) was prepared according to the literature.[81] In an oven-dried 8 mL screw-capped vial charged with a magnetic stirring bar, **3d** (61.2 mg, 0.2 mmol, 1 equiv.) and KHF_2 (51.5 mg, 0.66 mmol, 3.3 equiv.) were

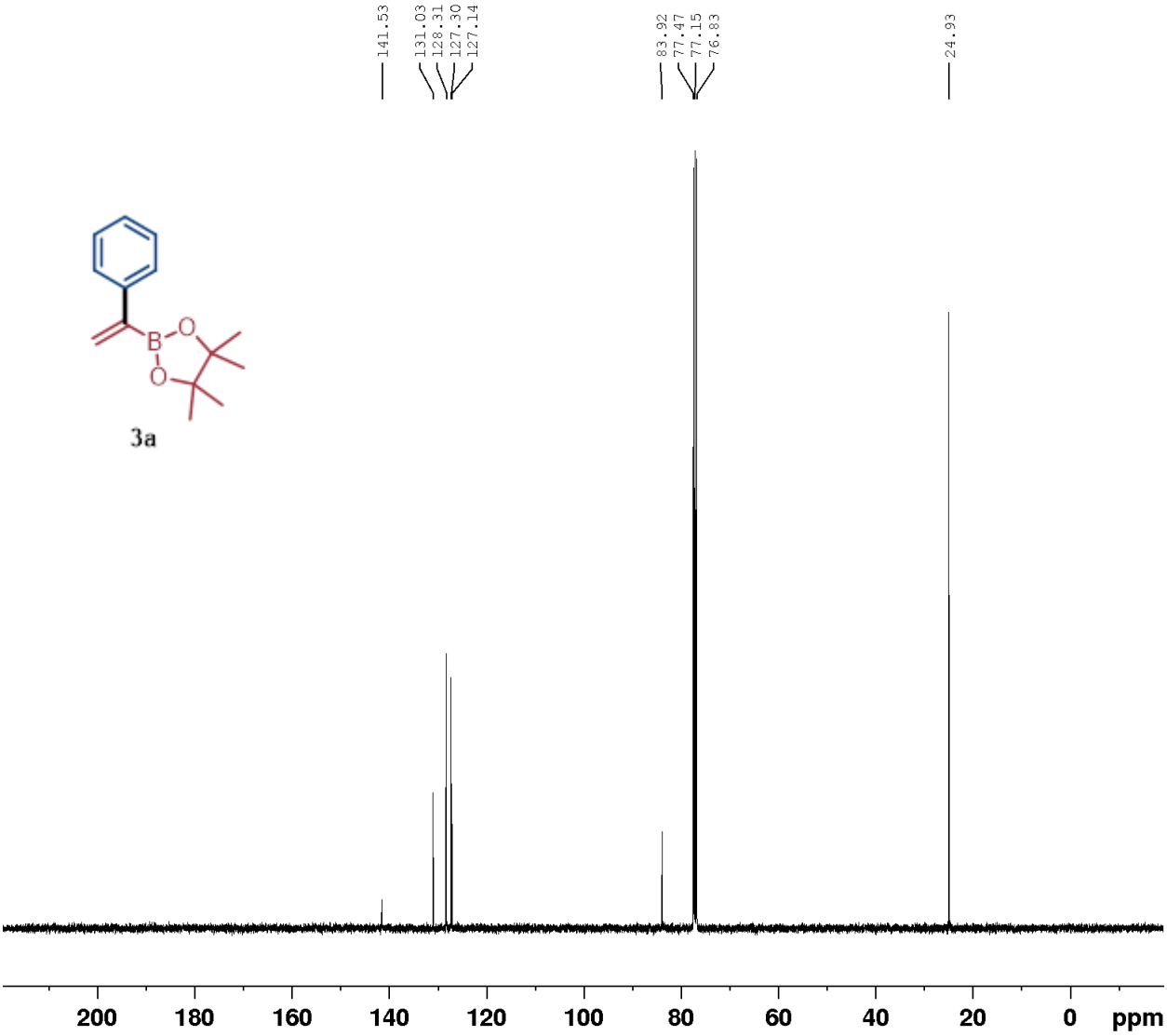
dissolved in a mixture of MeOH (2 mL) and water (0.1 mL). The reaction is allow to stir for 1 h at room temperature where the solution became white. The solvent was then removed by vacuum and the crude was dissolved using minimum amount of acetone. The solution is dried by $MgSO_4$ and vacuum filtered. The filtrate was concentrated by rotary evaporation to a saturation point. Et_2O was added to precipitated out the as a white crystalline solid, which was collected by vacuum filtration and further dried on the high vacuum (44 mg, 77%). **^{1}H NMR** (400 MHz, acetone-*d6*): δ (ppm) = 7.65-7.61 (m, 4H), 7.48-7.39 (m, 4H), 7.31-7.26 (m, 1H), 5.42-5.35 (m, 2H). **^{13}C NMR** (101 MHz, acetone-*d6*): δ (ppm) = 142.4, 138.2, 129.6, 129.5, 128.5, 127.4, 127.4, 126.6, 116.7. **^{19}F NMR** (283 MHz, acetone-*d6*): δ (ppm) = -141.4. **^{11}B NMR** (96 MHz, acetone-*d6*): δ (ppm) = 3.0. The carbon signal bound to the boron atom was not observed due to quadrupolar relaxation.

2.3.7 NMR spectra for α-vinylboronates and derivatized products

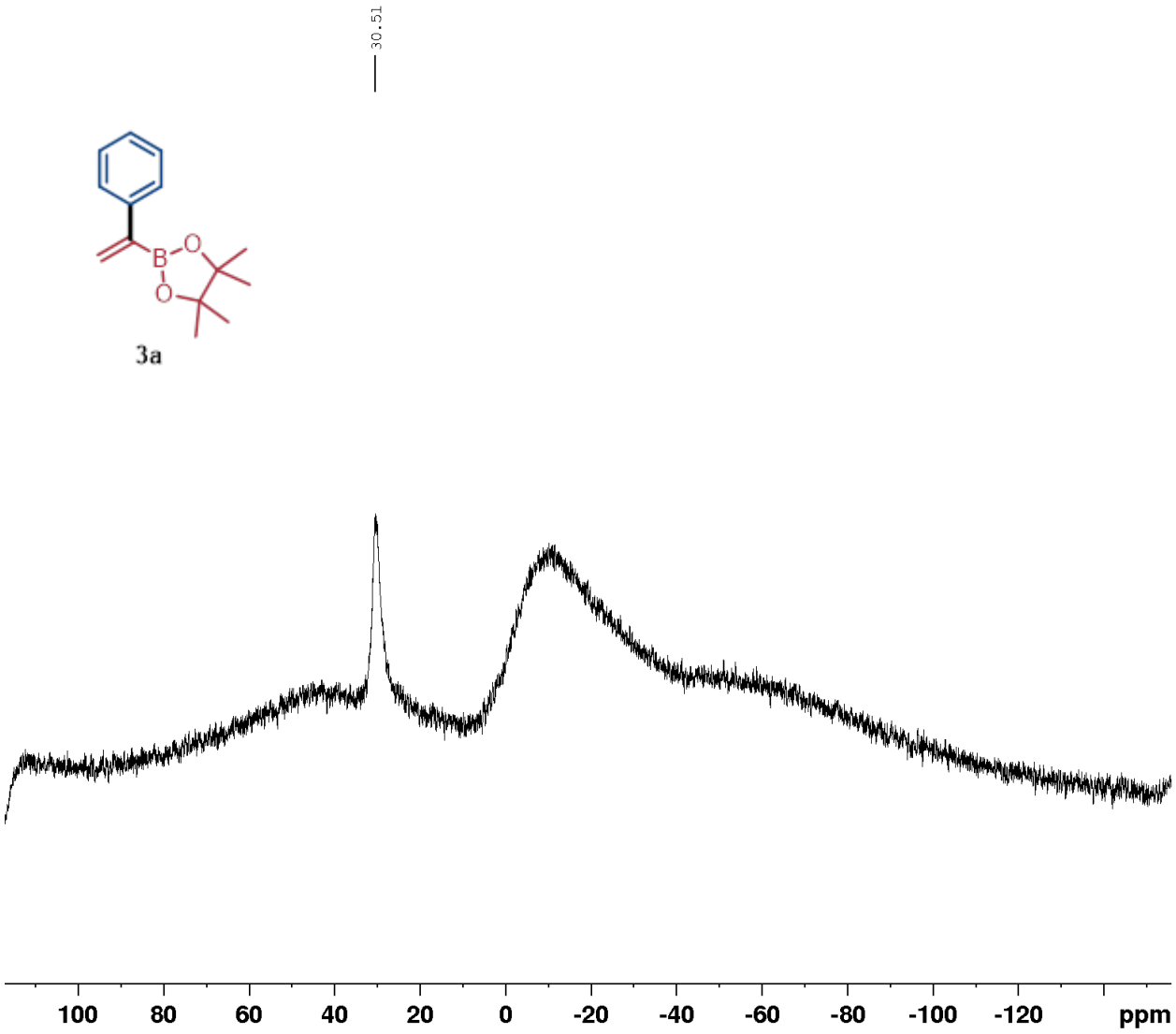
4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (3a), ^{1}H, $CDCl_3$, 400 MHz



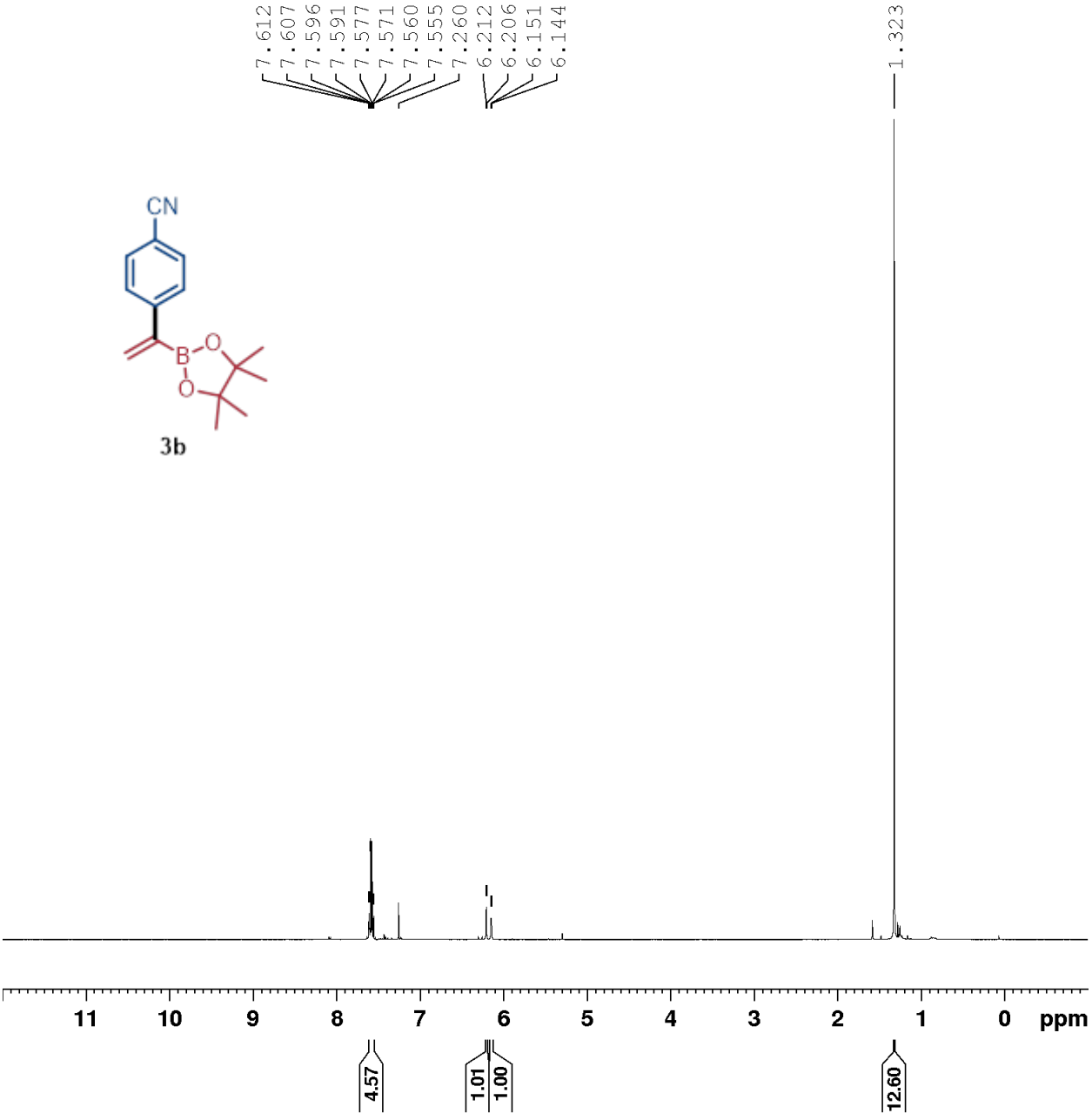
4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (3a), ^{13}C, $CDCl_3$, 101 MHz



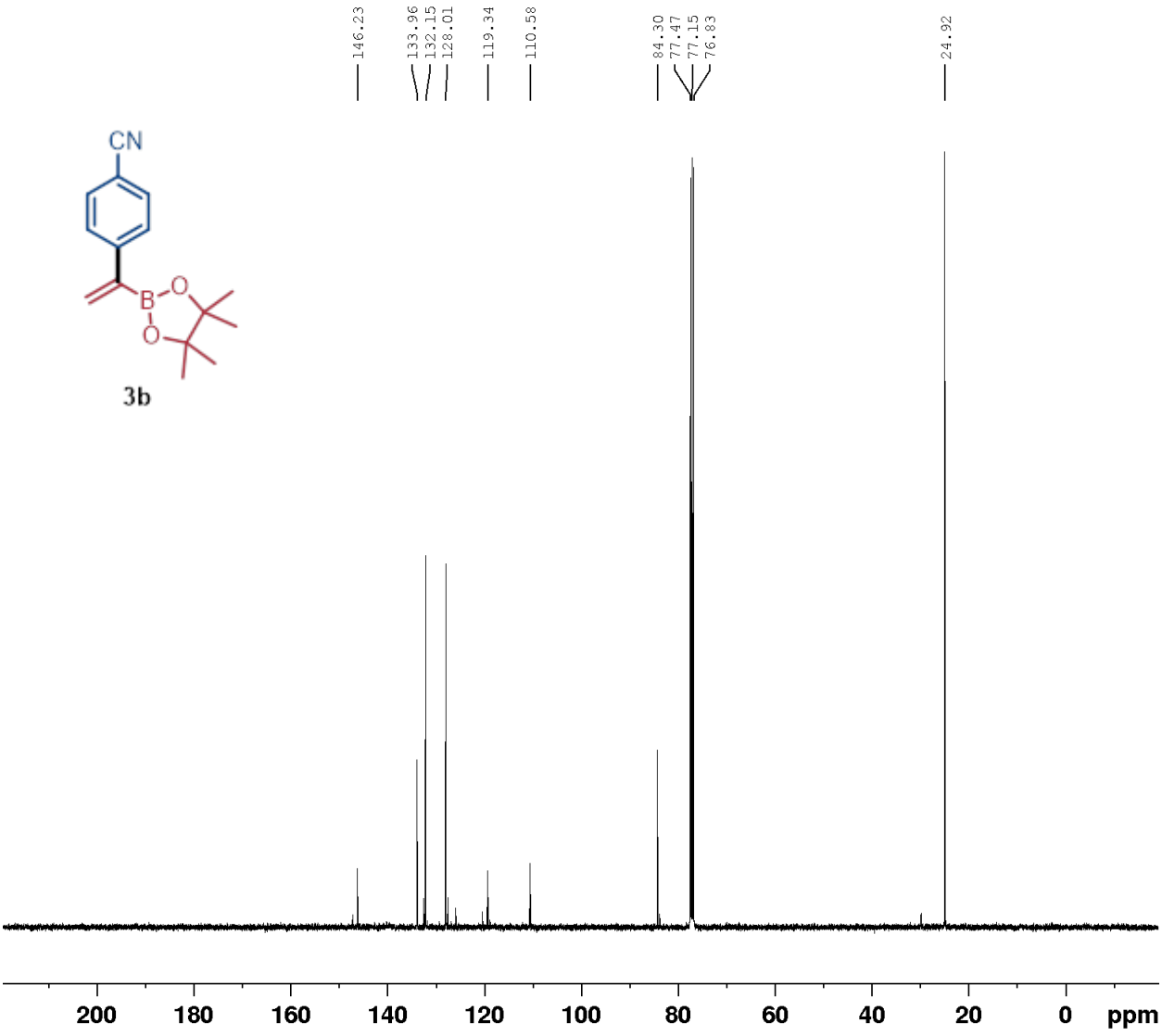
4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (3a), ^{11}B, $CDCl_3$, 96 MHz



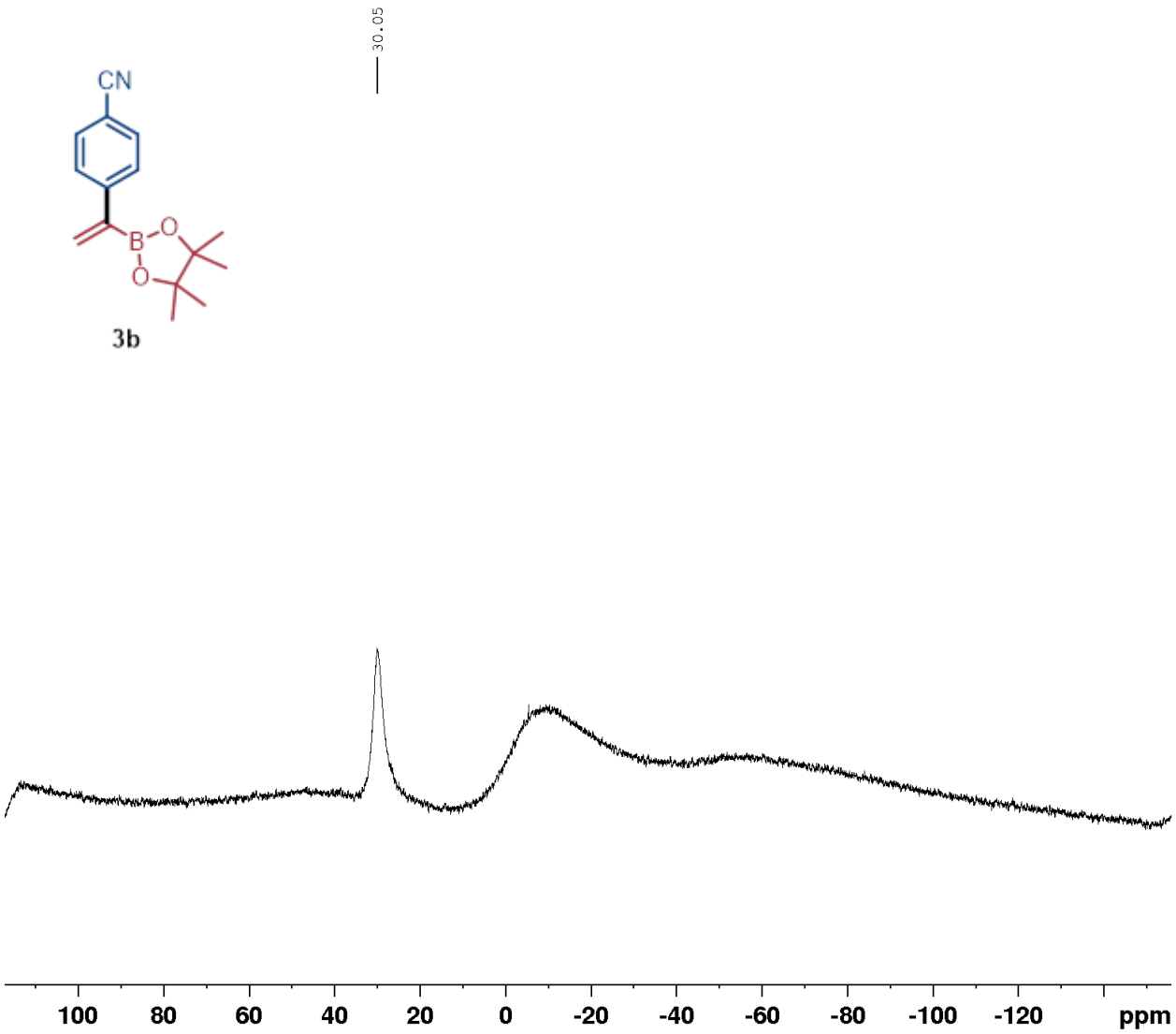
4,4,5,5-tetramethyl-2-(1-(4-cyanophenyl)vinyl)-1,3,2-dioxaborolane (3b), ^{1}H, $CDCl_3$, 400 MHz



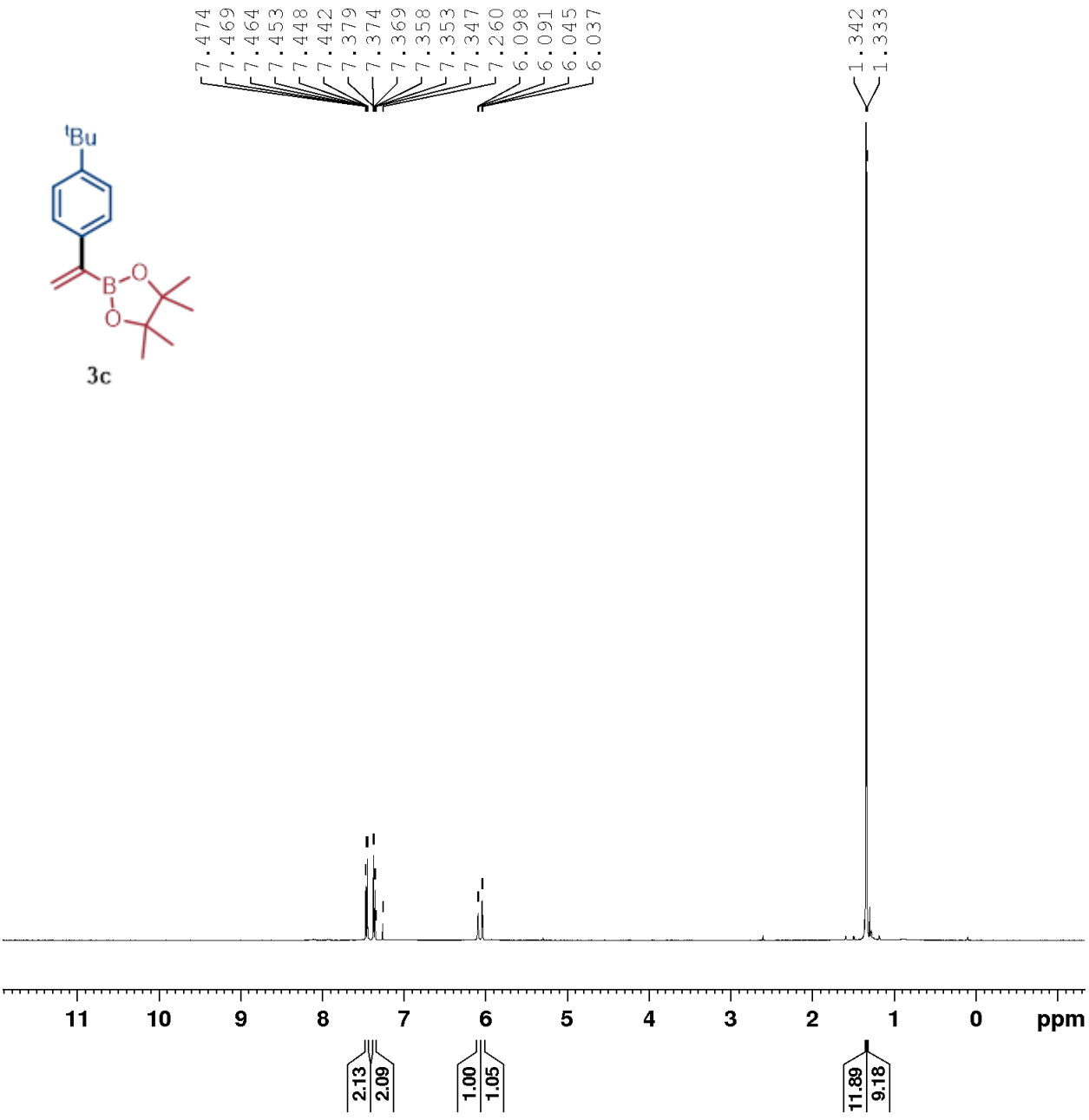
4,4,5,5-tetramethyl-2-(1-(4-cyanophenyl)vinyl)-1,3,2-dioxaborolane (3b), ^{13}C, $CDCl_3$, 101 MHz



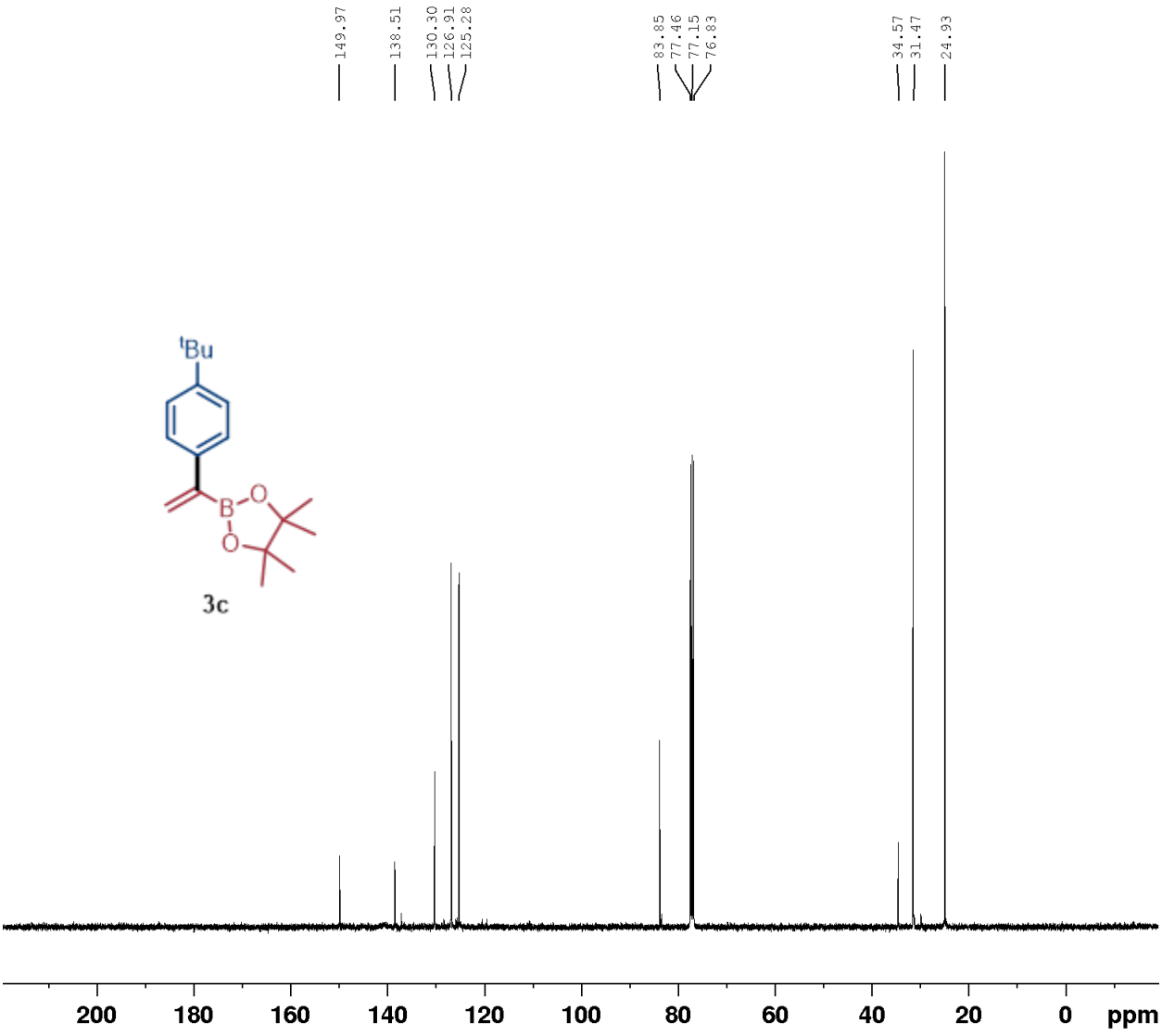
4,4,5,5-tetramethyl-2-(1-(4-cyanophenyl)vinyl)-1,3,2-dioxaborolane (3b), ^{11}B, $CDCl_3$, 96 MHz



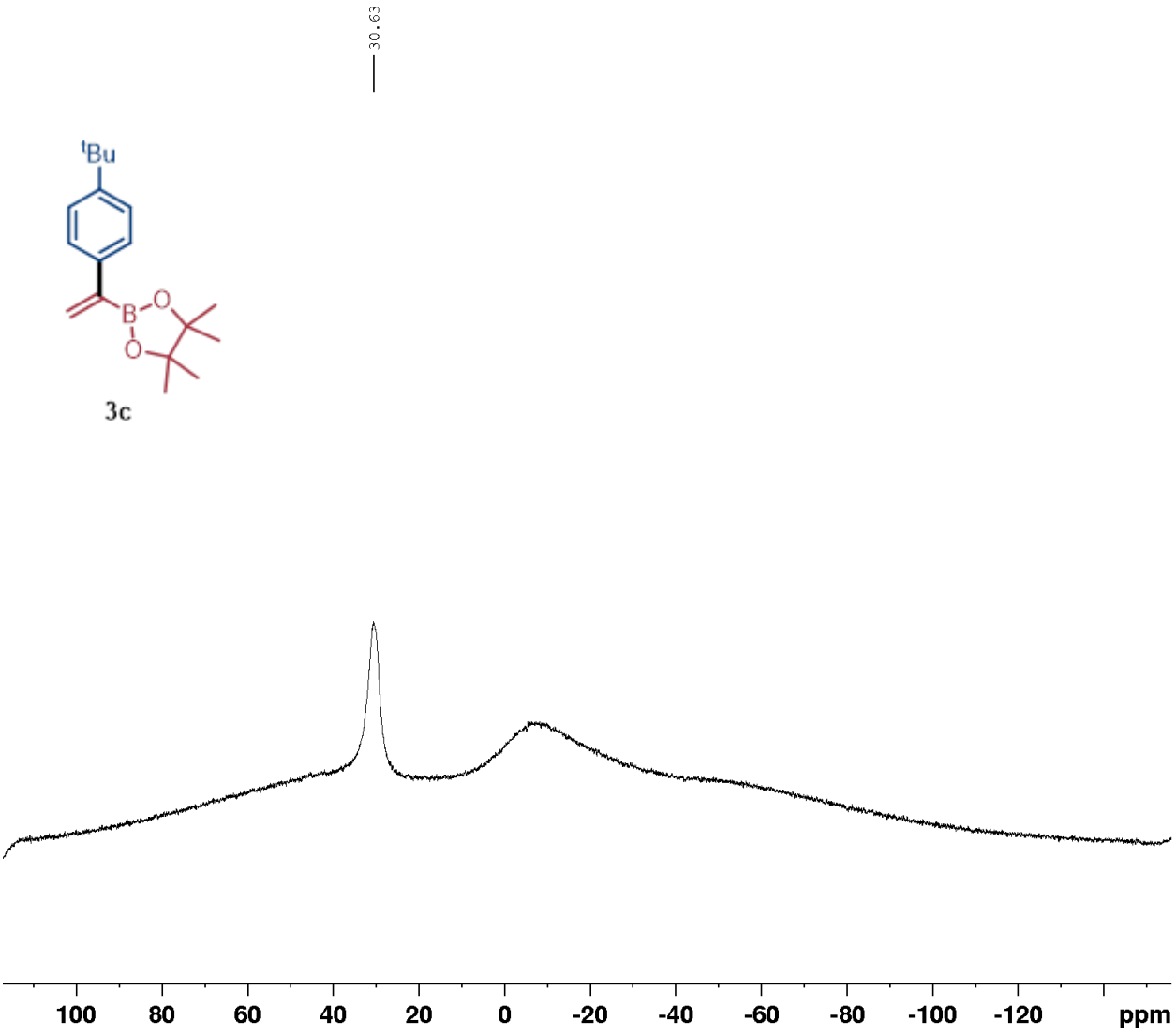
4,4,5,5-tetramethyl-2-(1-(4-tert-butylphenyl)vinyl)-1,3,2-dioxaborolane (3c), ^{1}H, $CDCl_3$, 400 MHz



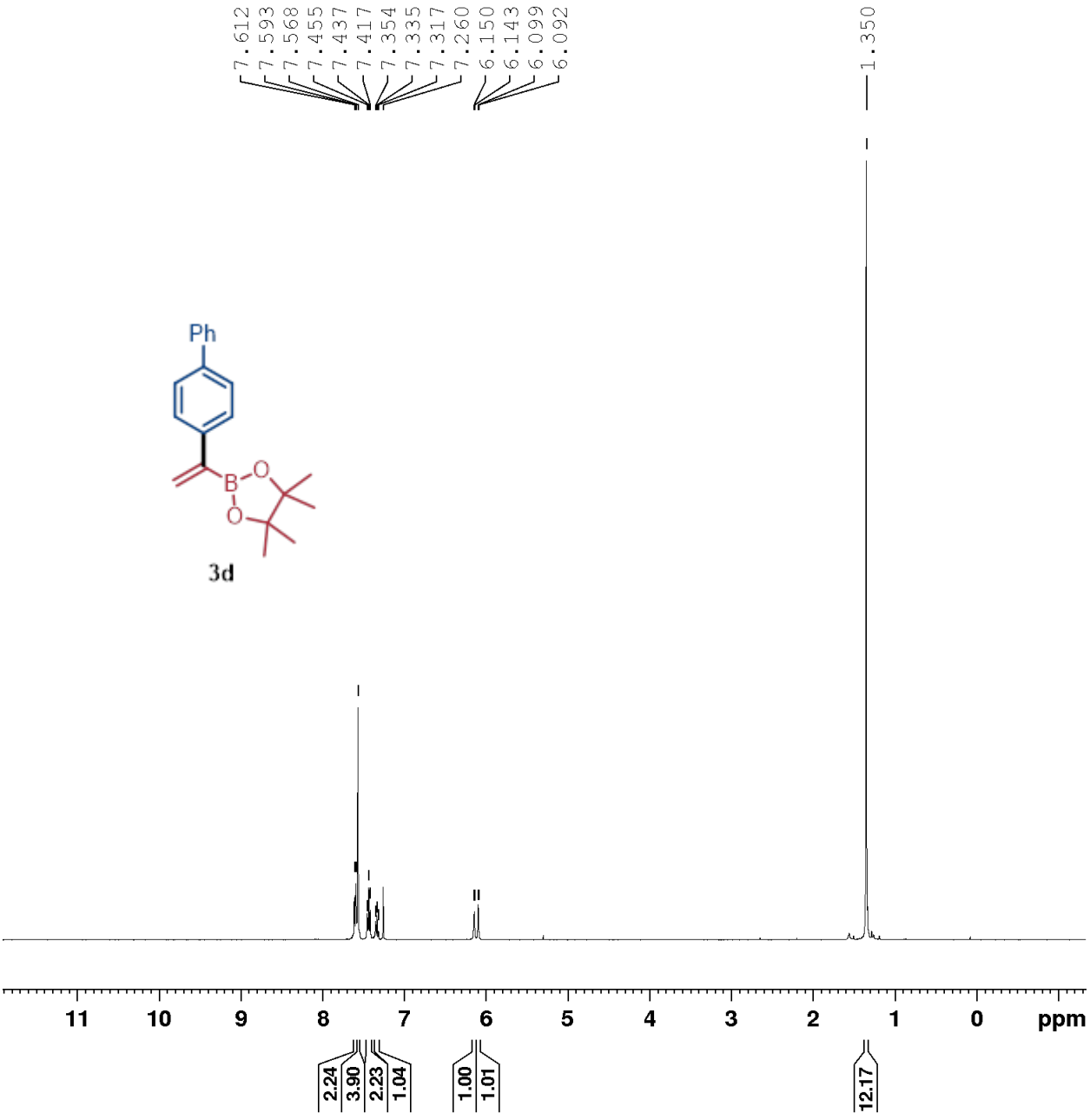
4,4,5,5-tetramethyl-2-(1-(4-tert-butylphenyl)vinyl)-1,3,2-dioxaborolane (3c), ^{13}C, $CDCl_3$, 101 MHz



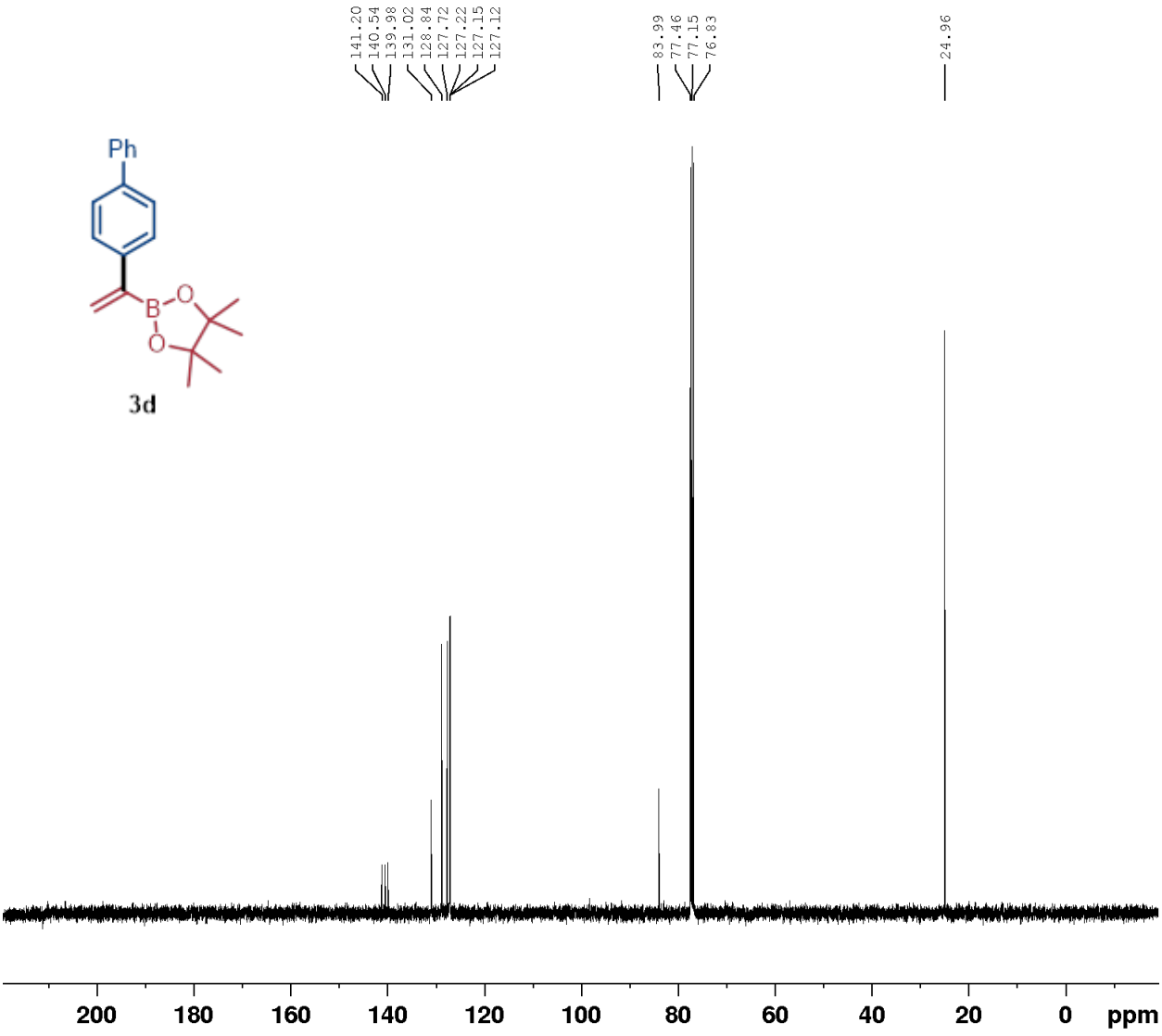
4,4,5,5-tetramethyl-2-(1-(4-tert-butylphenyl)vinyl)-1,3,2-dioxaborolane (3c), ^{11}B, $CDCl_3$, 96 MHz



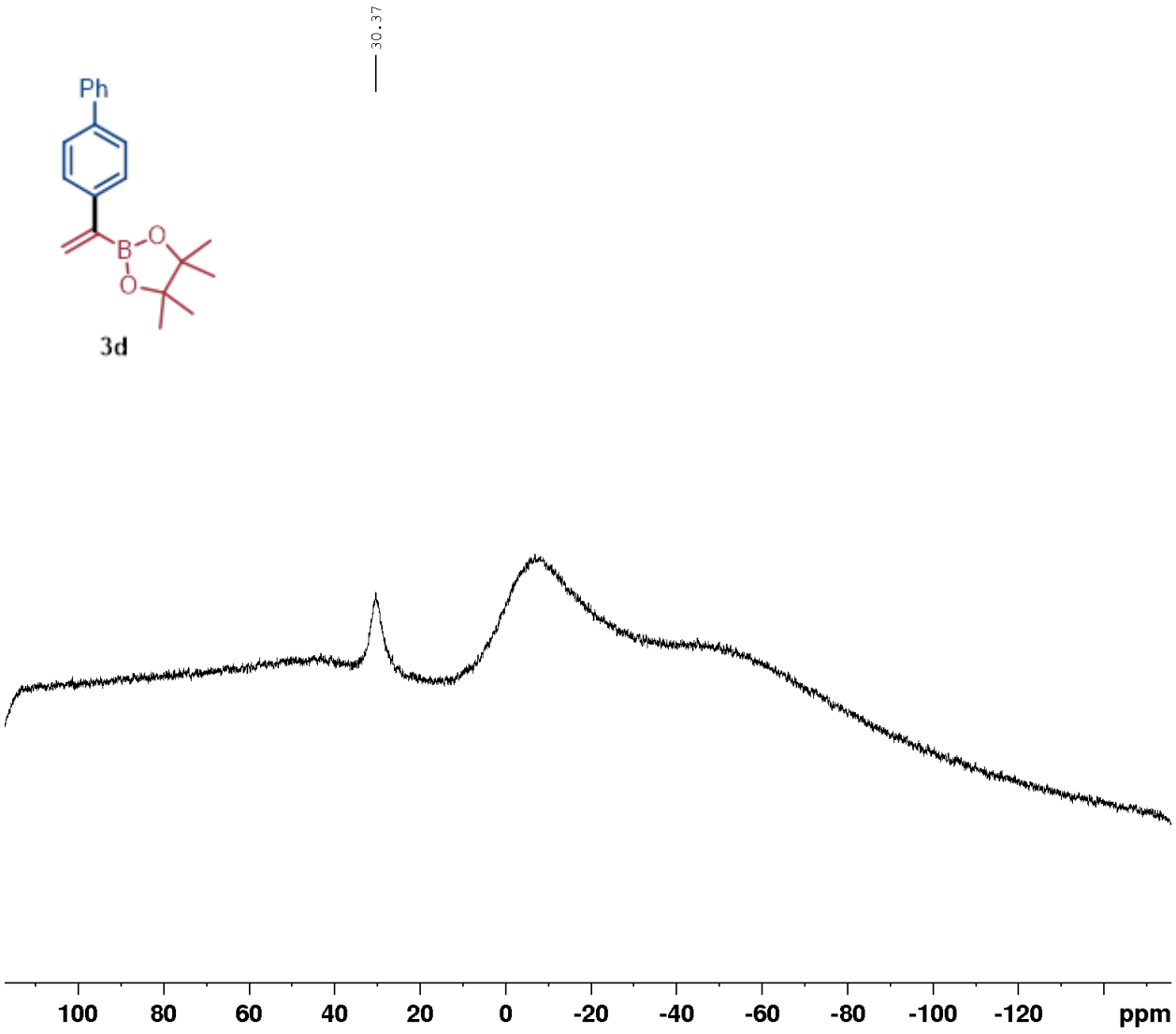
4,4,5,5-tetramethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborolane (3d), ^{1}H, $CDCl_3$, 400 MHz



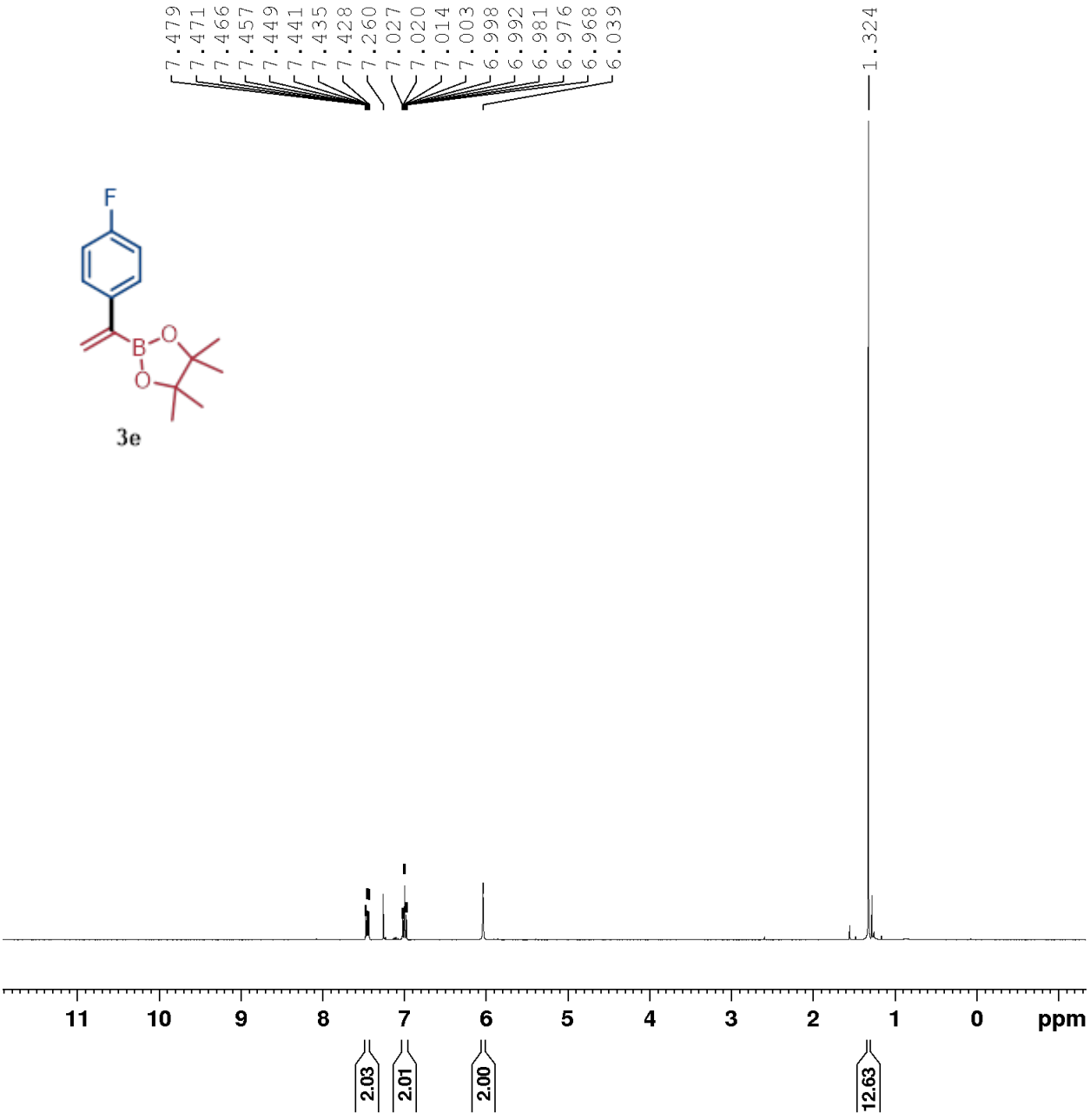
4,4,5,5-tetramethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborolane (3d), ^{13}C, $CDCl_3$, 101 MHz



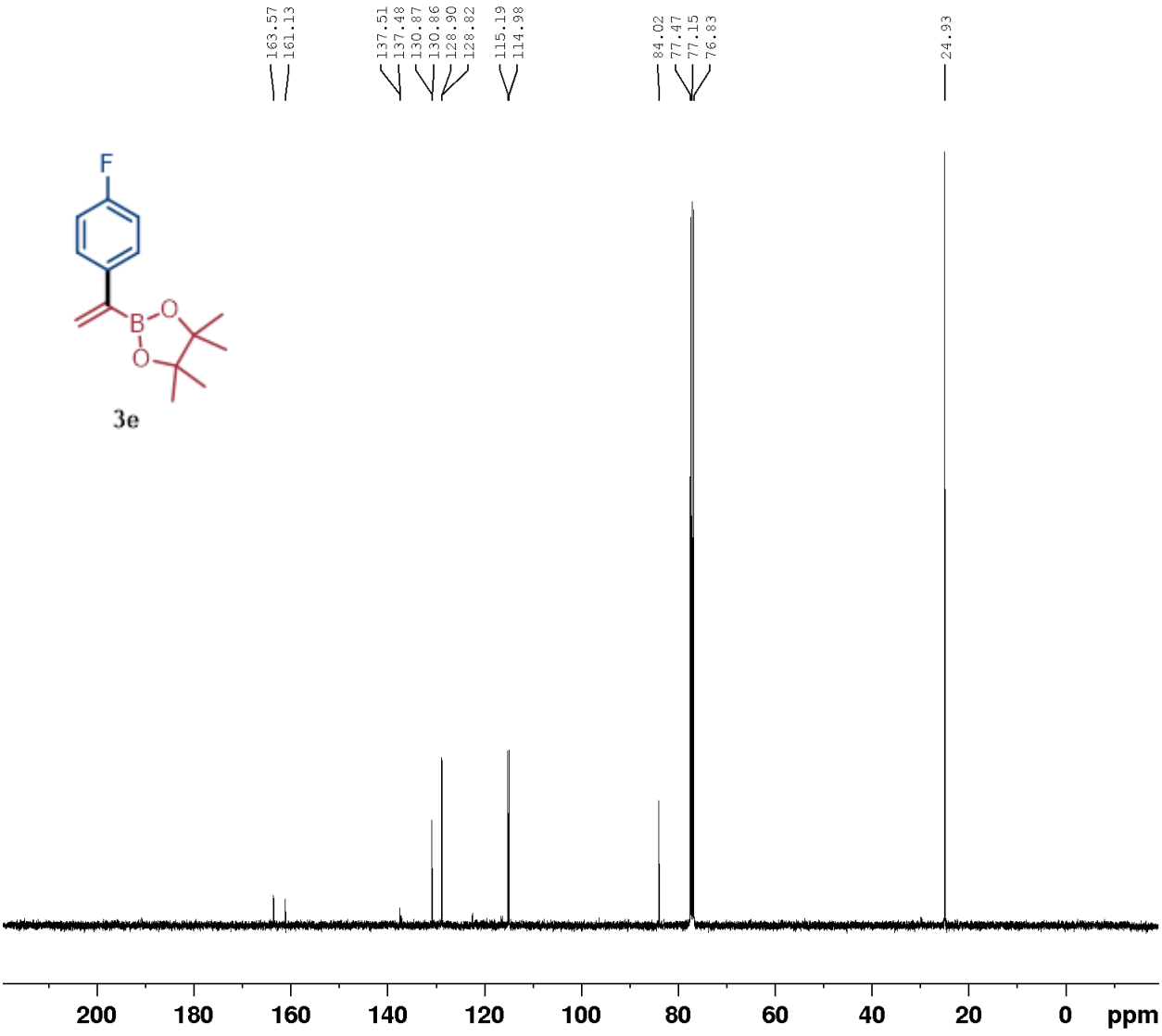
4,4,5,5-tetramethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborolane (3d), ^{11}B, $CDCl_3$, 96 MHz



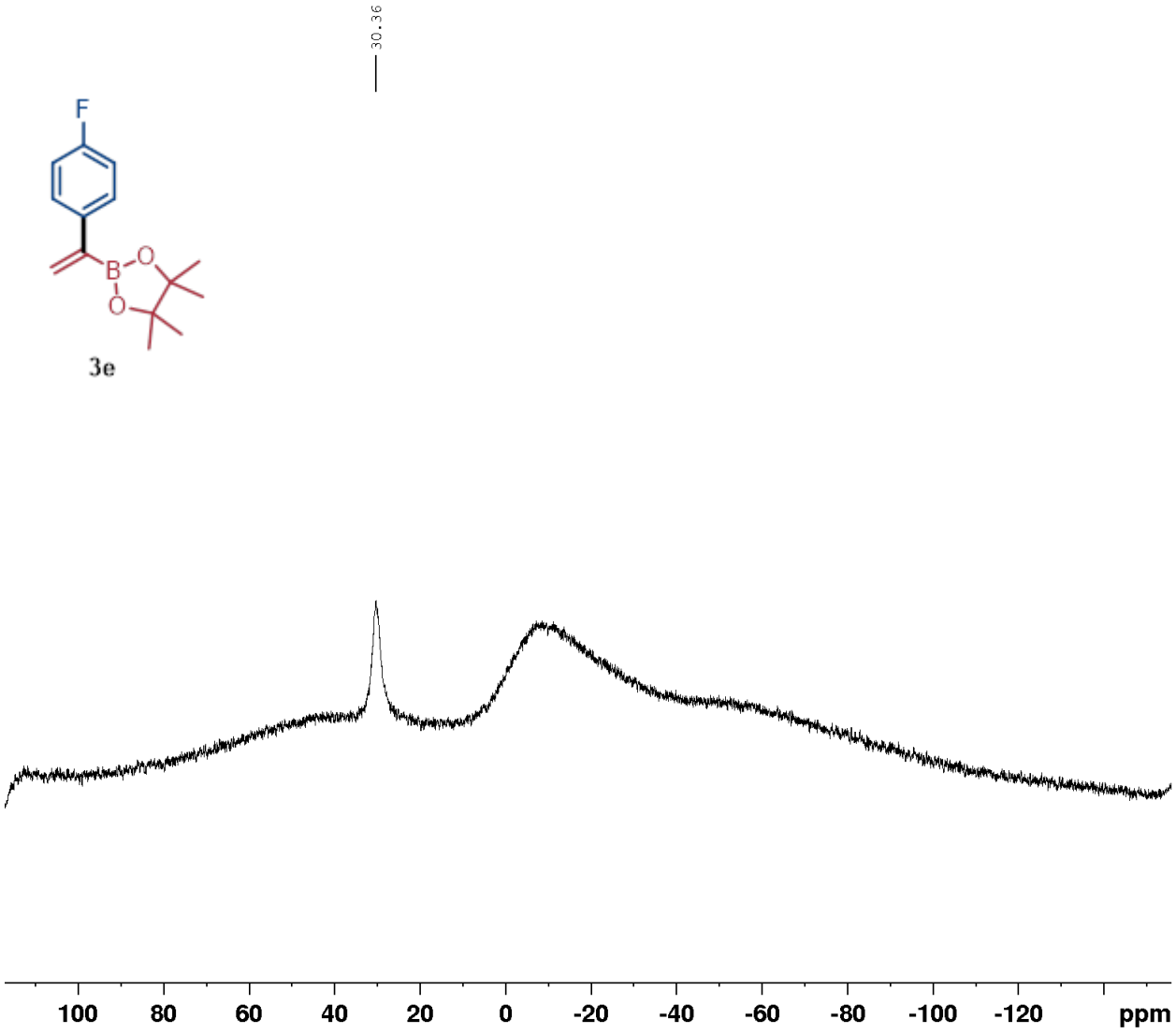
4,4,5,5-tetramethyl-2-(1-(4-fluorophenyl)vinyl)-1,3,2-dioxaborolane (3e), ^{1}H, $CDCl_3$, 400 MHz



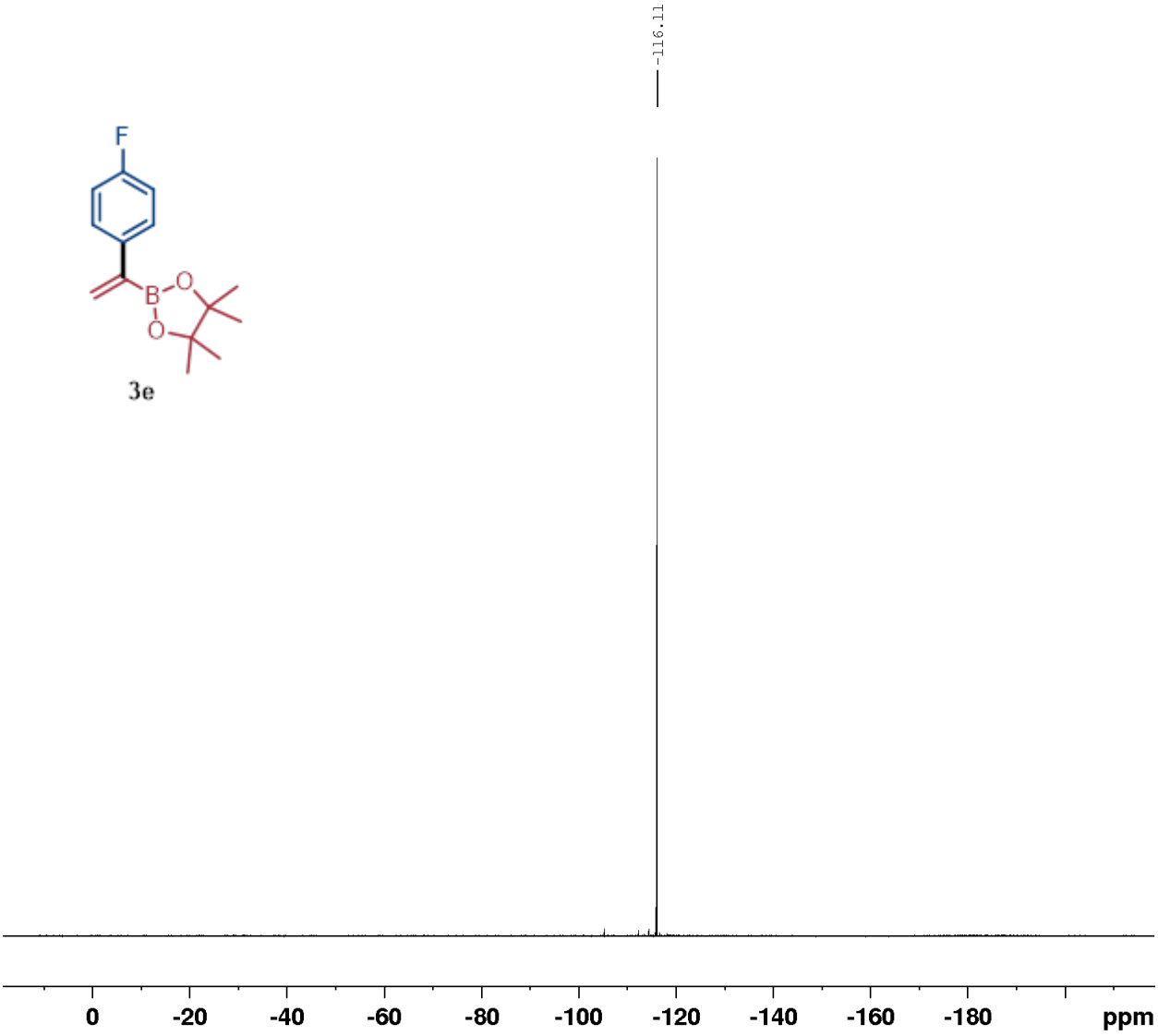
4,4,5,5-tetramethyl-2-(1-(4-fluorophenyl)vinyl)-1,3,2-dioxaborolane (3e), ^{13}C, $CDCl_3$, 101 MHz



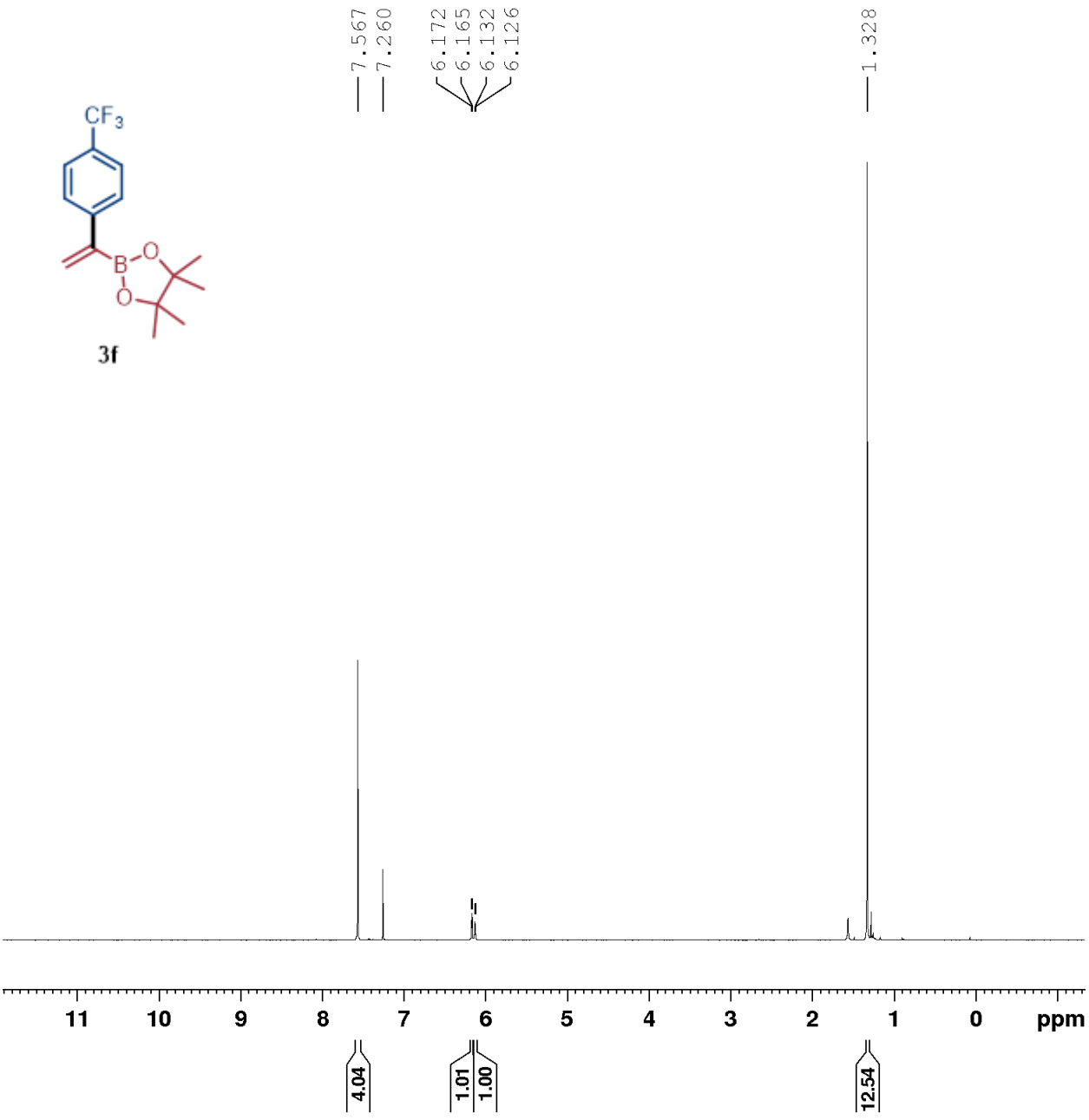
4,4,5,5-tetramethyl-2-(1-(4-fluorophenyl)vinyl)-1,3,2-dioxaborolane (3e), ^{11}B, $CDCl_3$, 96 MHz



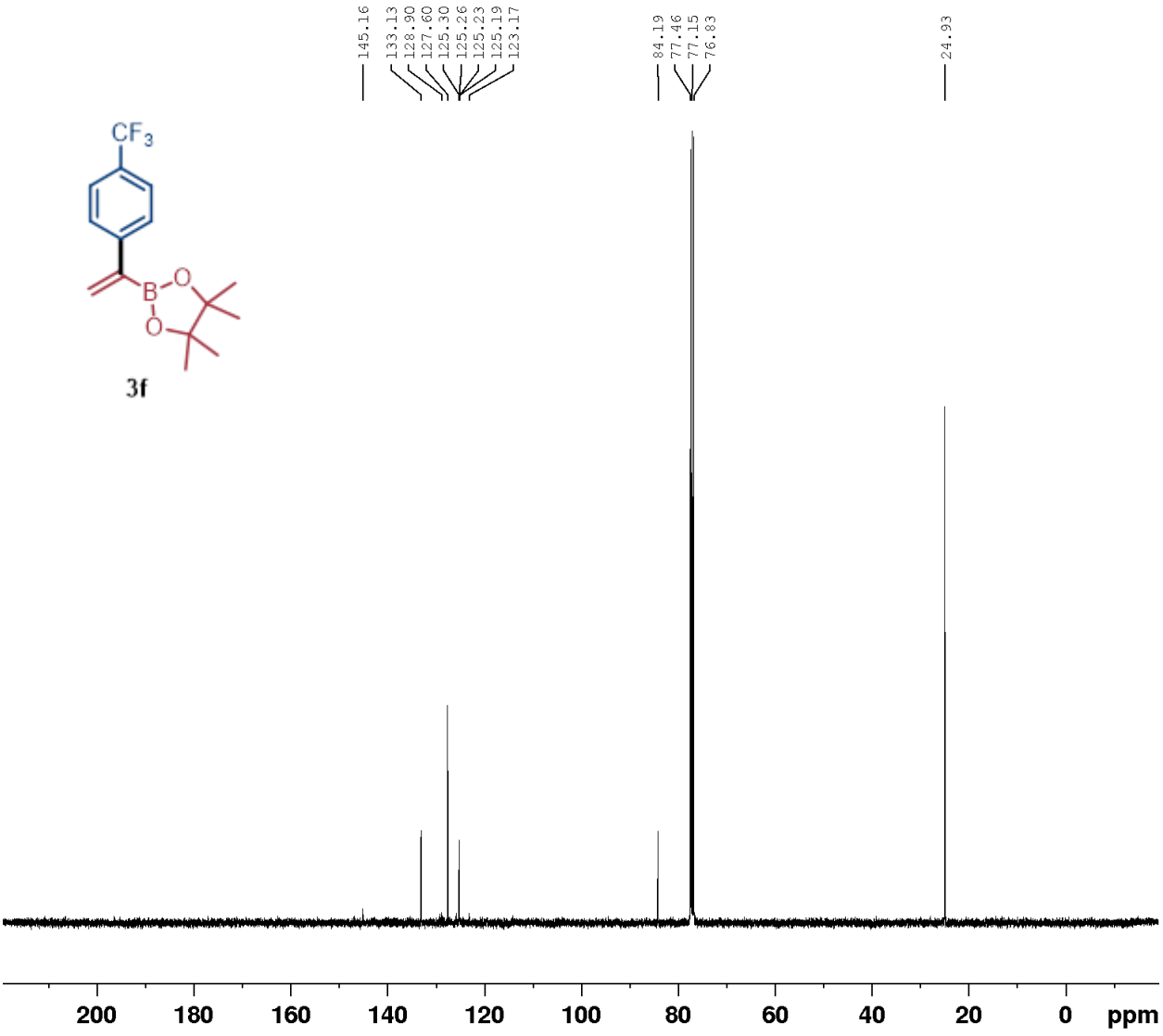
4,4,5,5-tetramethyl-2-(1-(4-fluorophenyl)vinyl)-1,3,2-dioxaborolane (3e), ^{19}F, $CDCl_3$, 283 MHz



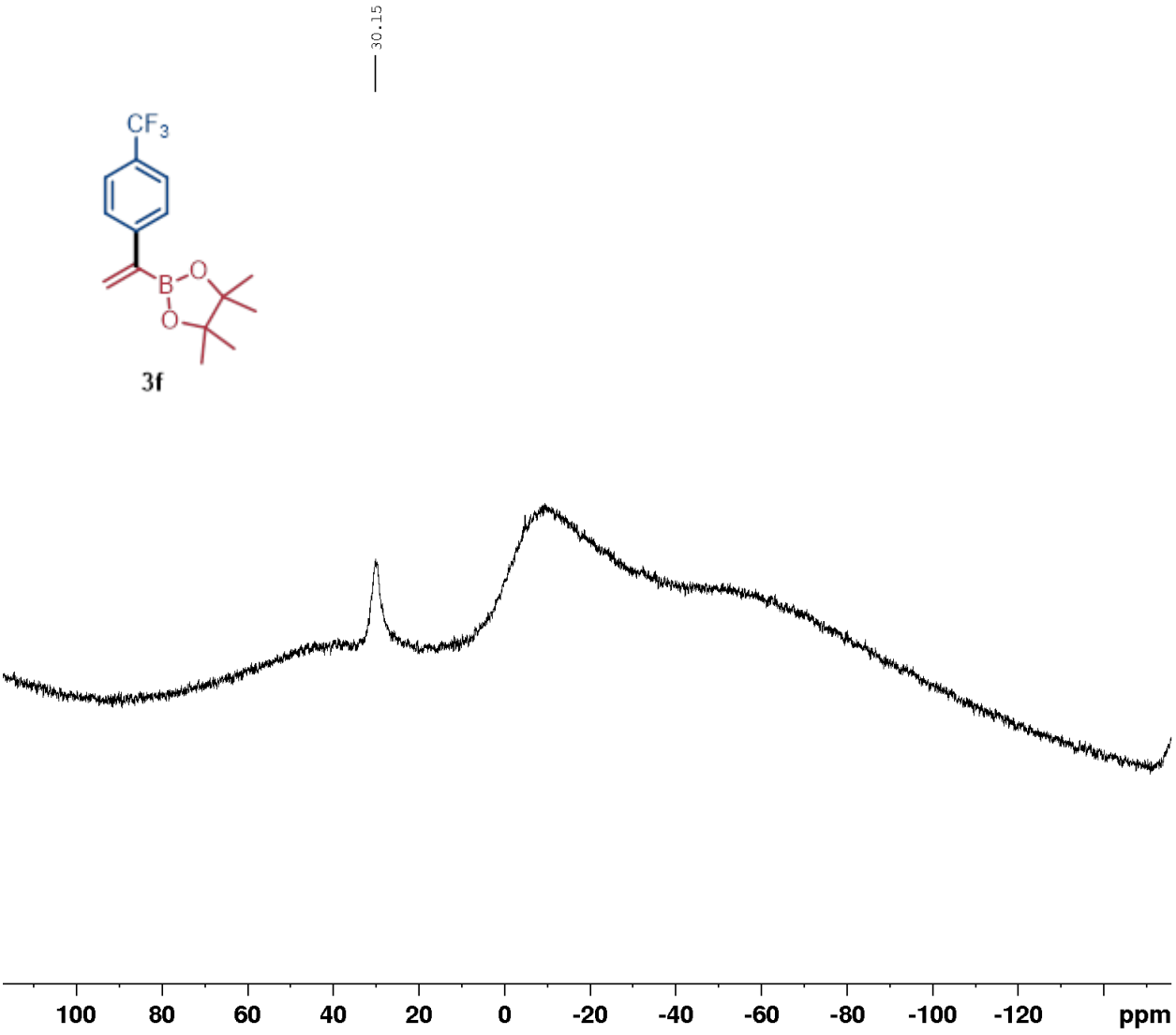
4,4,5,5-tetramethyl-2-(1-(4-trifluoromethylphenyl)vinyl)-1,3,2-dioxaborolane (3f), ^{1}H, $CDCl_3$, 400 MHz



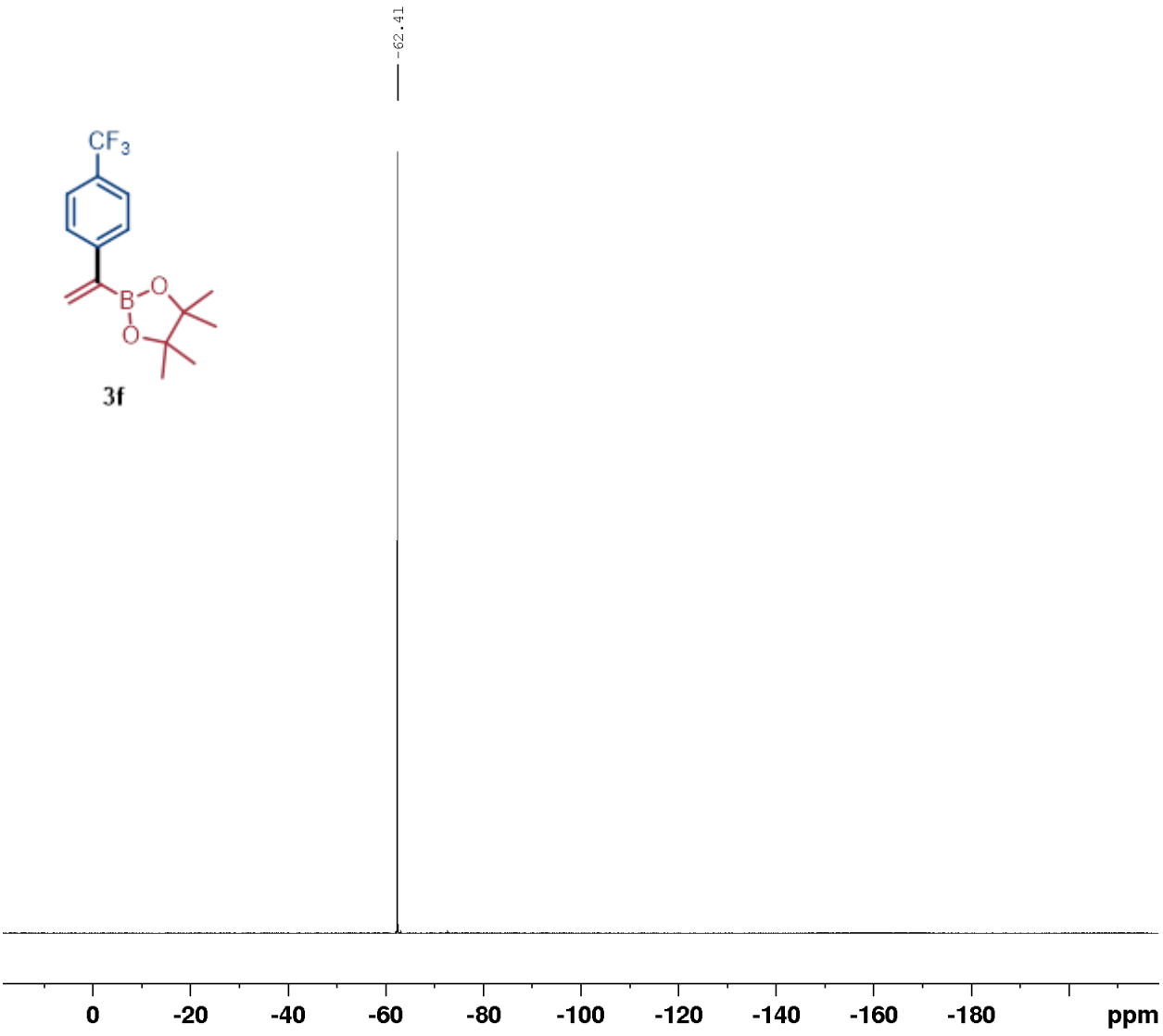
4,4,5,5-tetramethyl-2-(1-(4-trifluoromethylphenyl)vinyl)-1,3,2-dioxaborolane (3f), ^{13}C, $CDCl_3$, 101 MHz



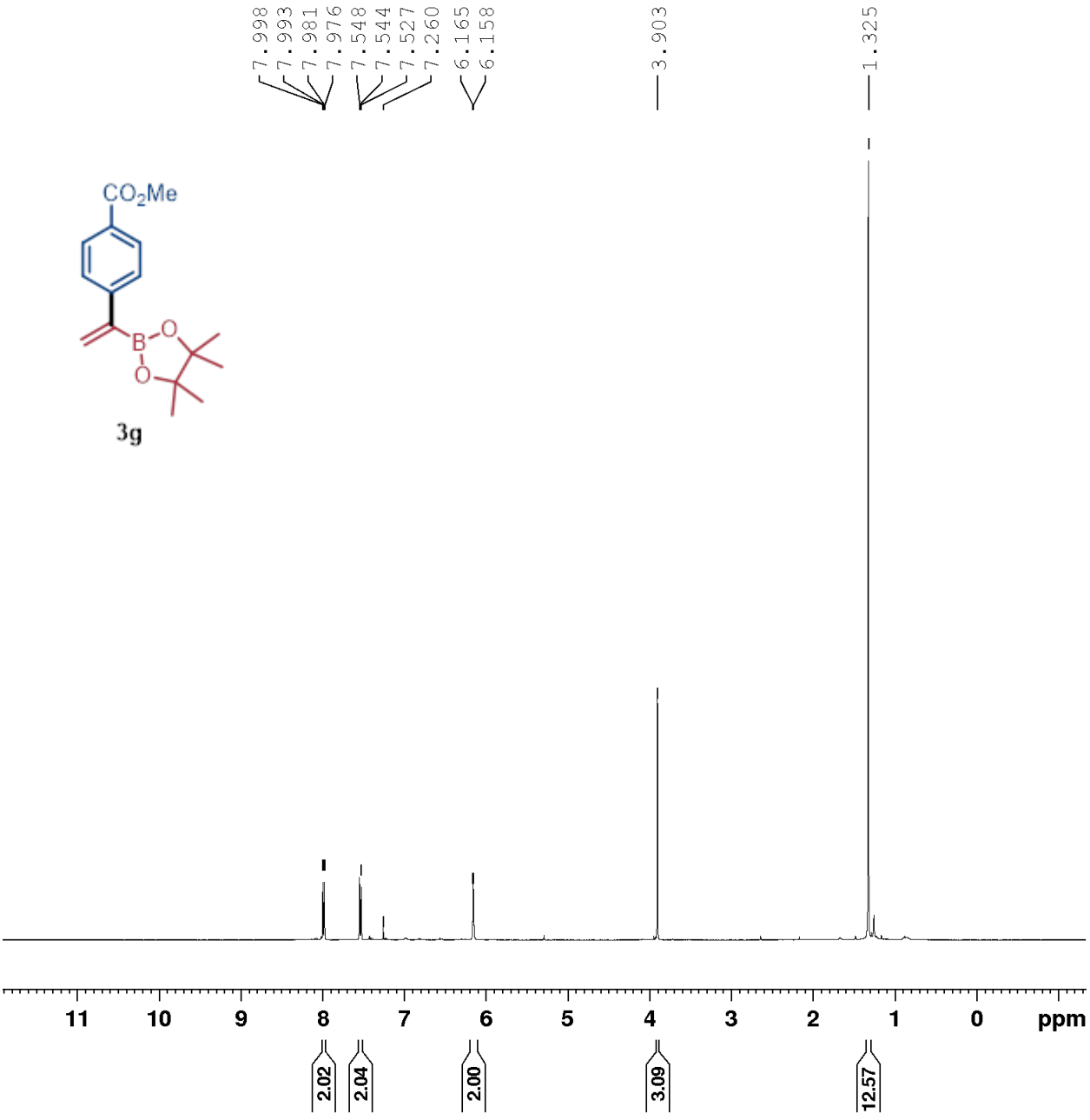
4,4,5,5-tetramethyl-2-(1-(4-trifluoromethylphenyl)vinyl)-1,3,2-dioxaborolane (3f), ^{11}B, $CDCl_3$, 96 MHz



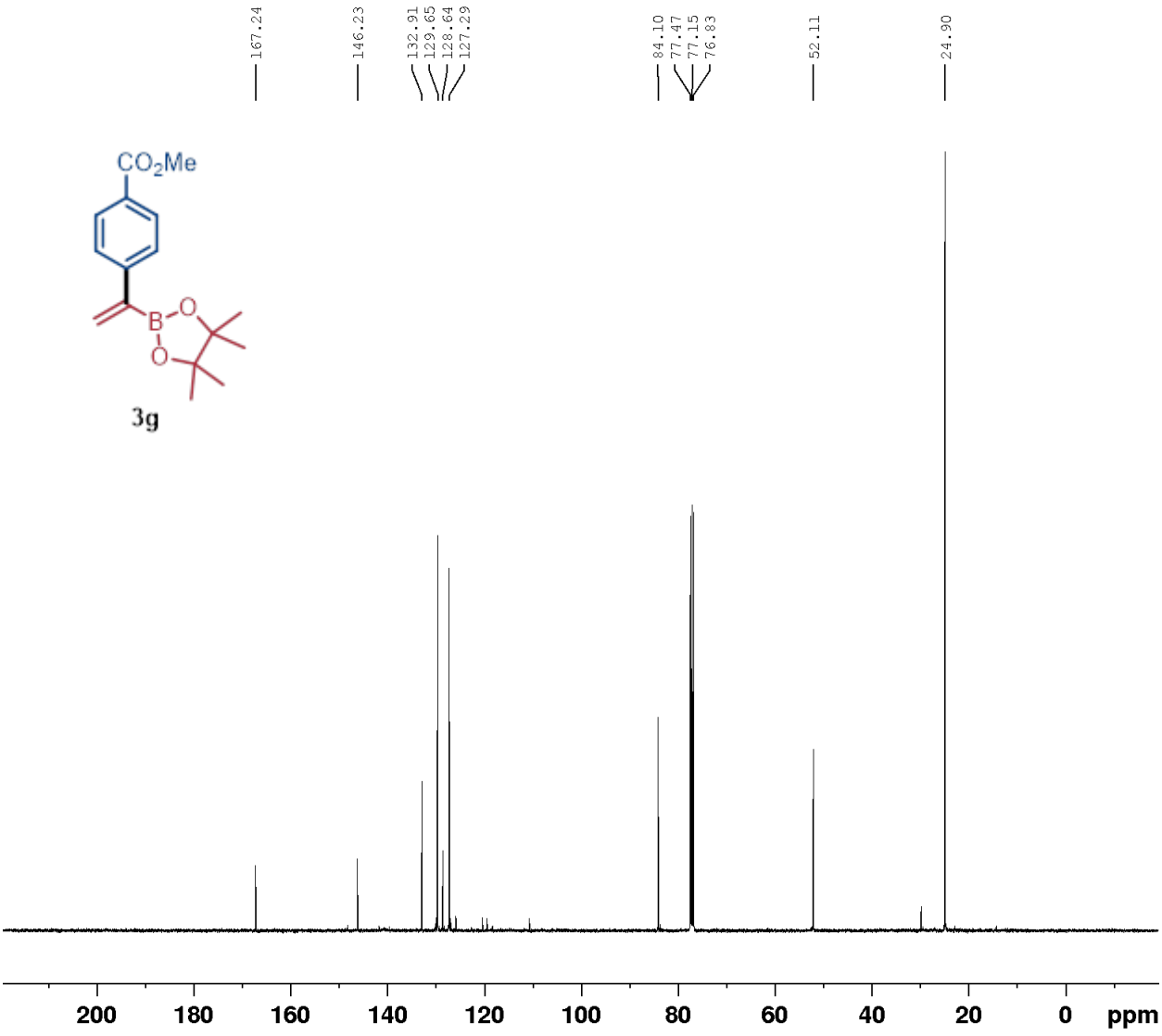
4,4,5,5-tetramethyl-2-(1-(4-trifluoromethylphenyl)vinyl)-1,3,2-dioxaborolane (3f), ^{19}F, $CDCl_3$, 283 MHz



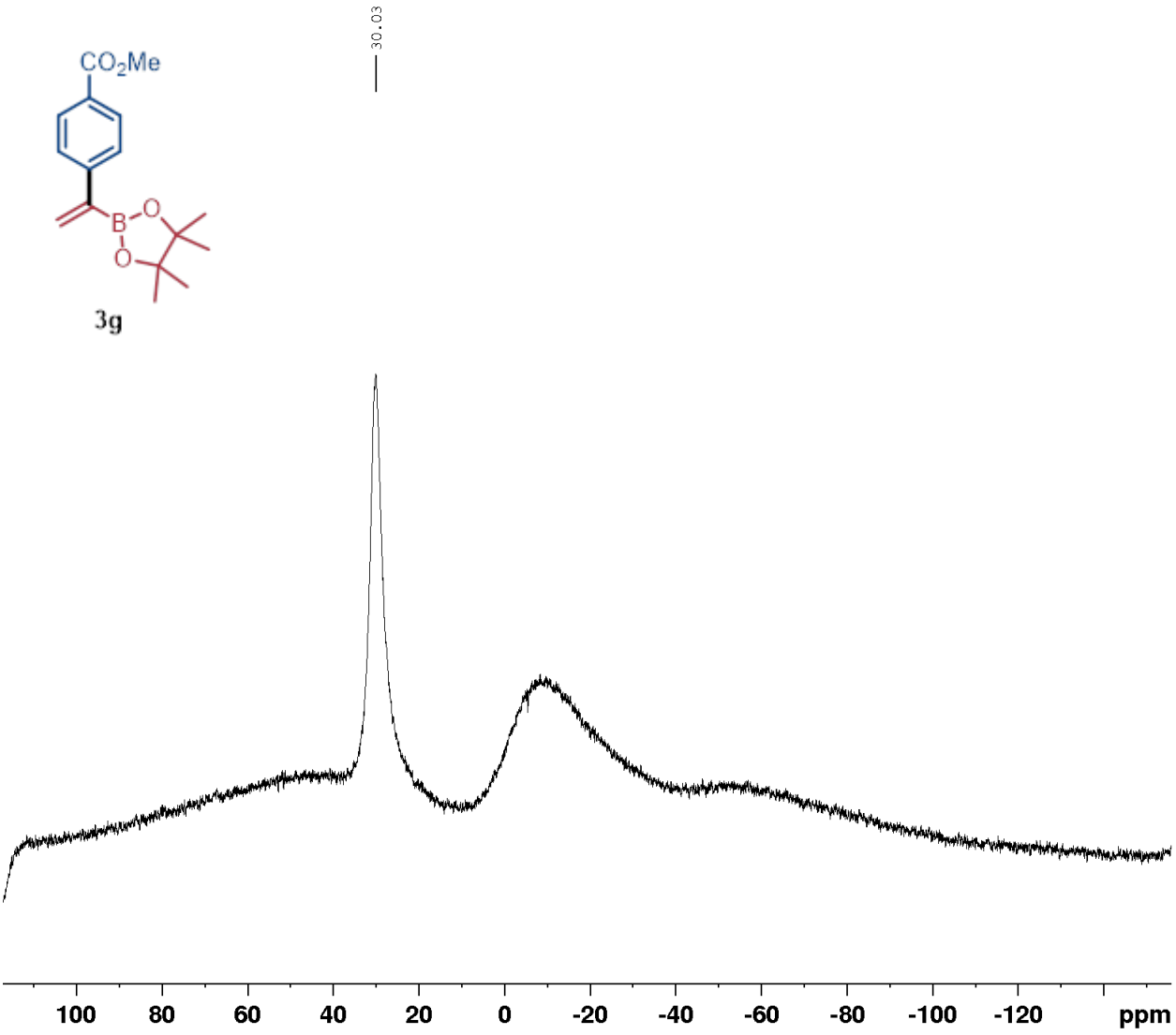
methyl 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzoate (3g), ^{1}H, $CDCl_3$, 400 MHz



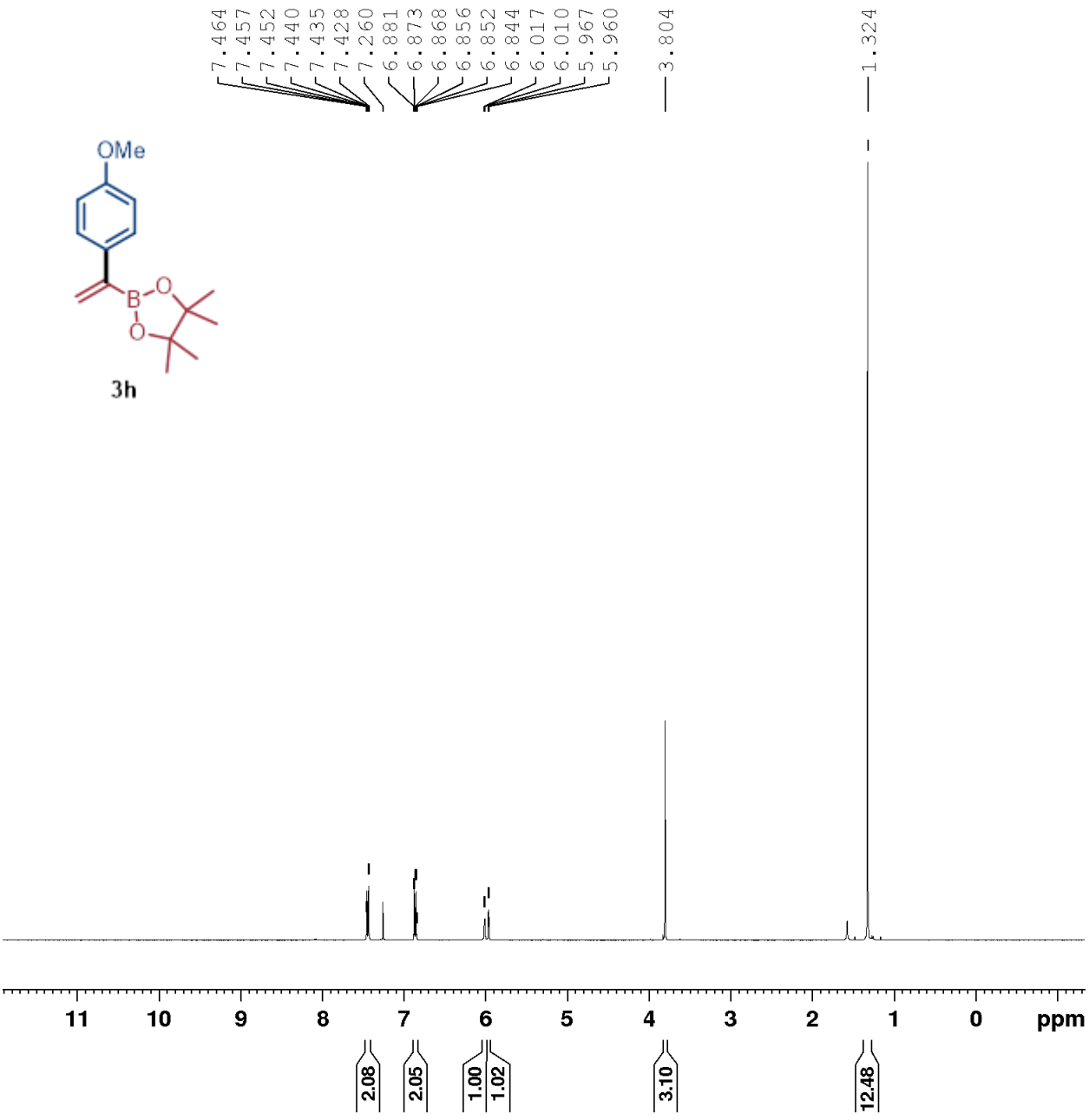
methyl 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzoate (3g), ^{13}C, $CDCl_3$, 101 MHz



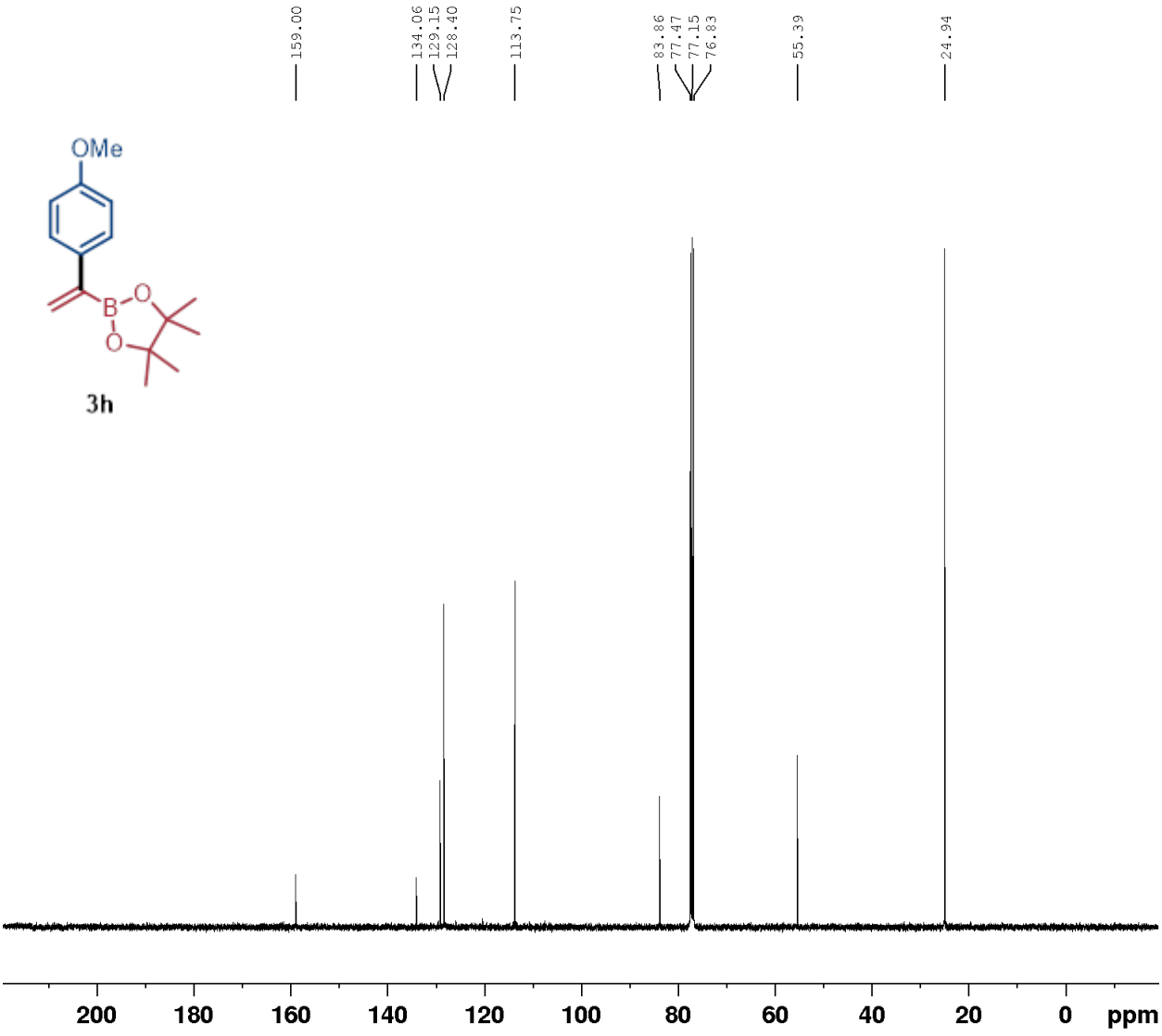
methyl 4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)benzoate (3g), ^{11}B, $CDCl_3$, 96 MHz



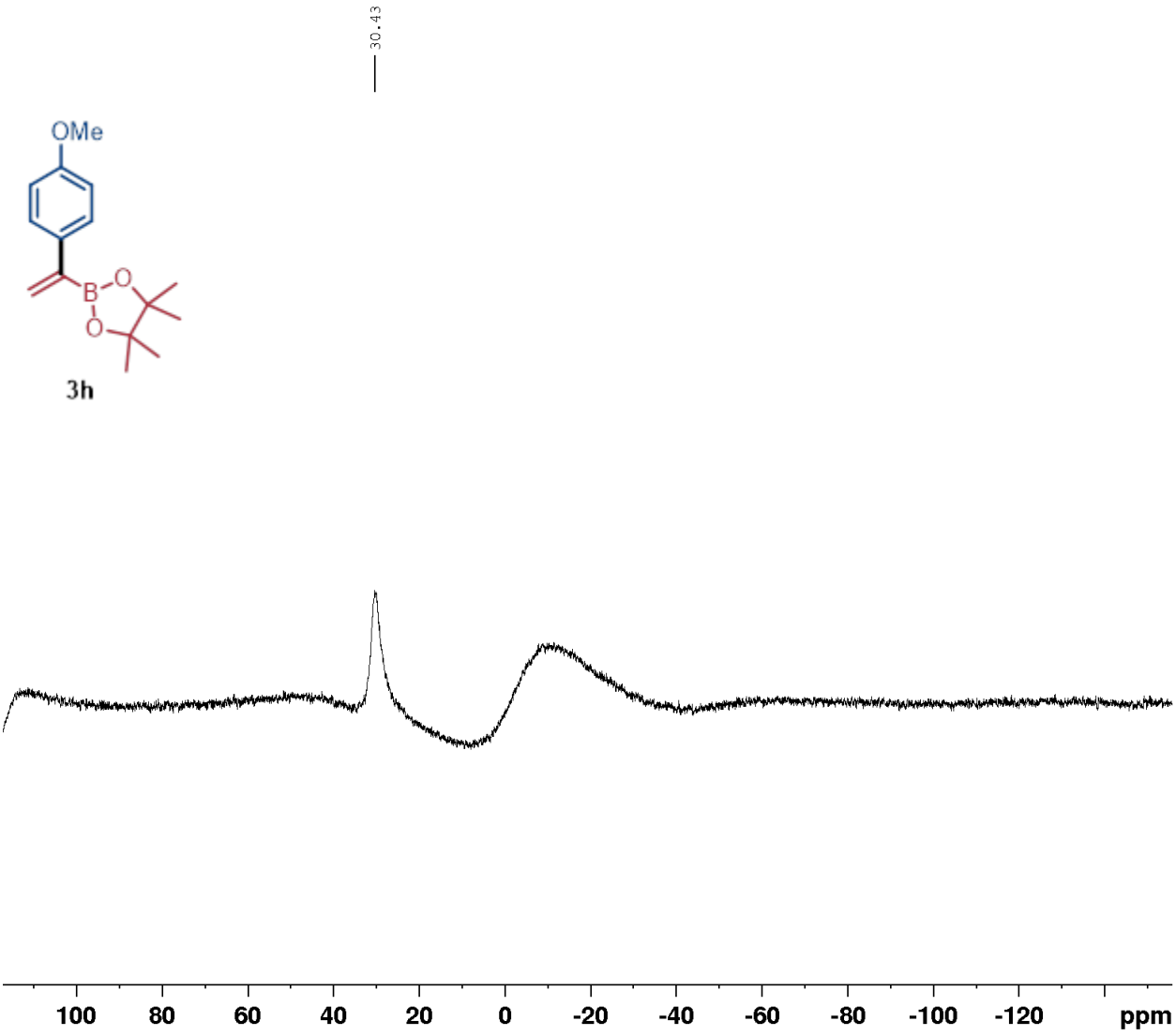
4,4,5,5-tetramethyl-2-(1-(4-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3h), ^{1}H, $CDCl_3$, 400 MHz



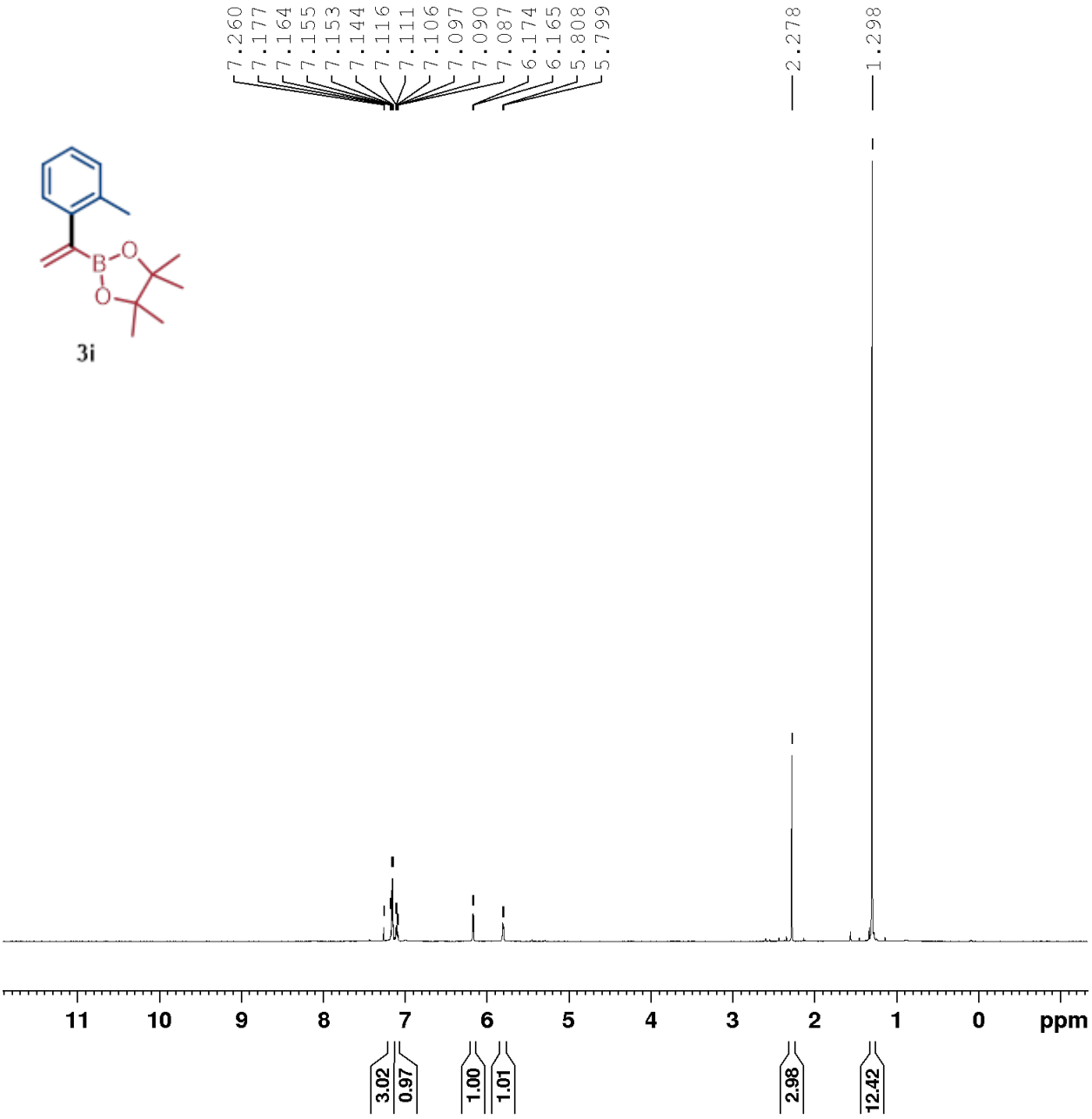
4,4,5,5-tetramethyl-2-(1-(4-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3h), ^{13}C, $CDCl_3$, 101 MHz



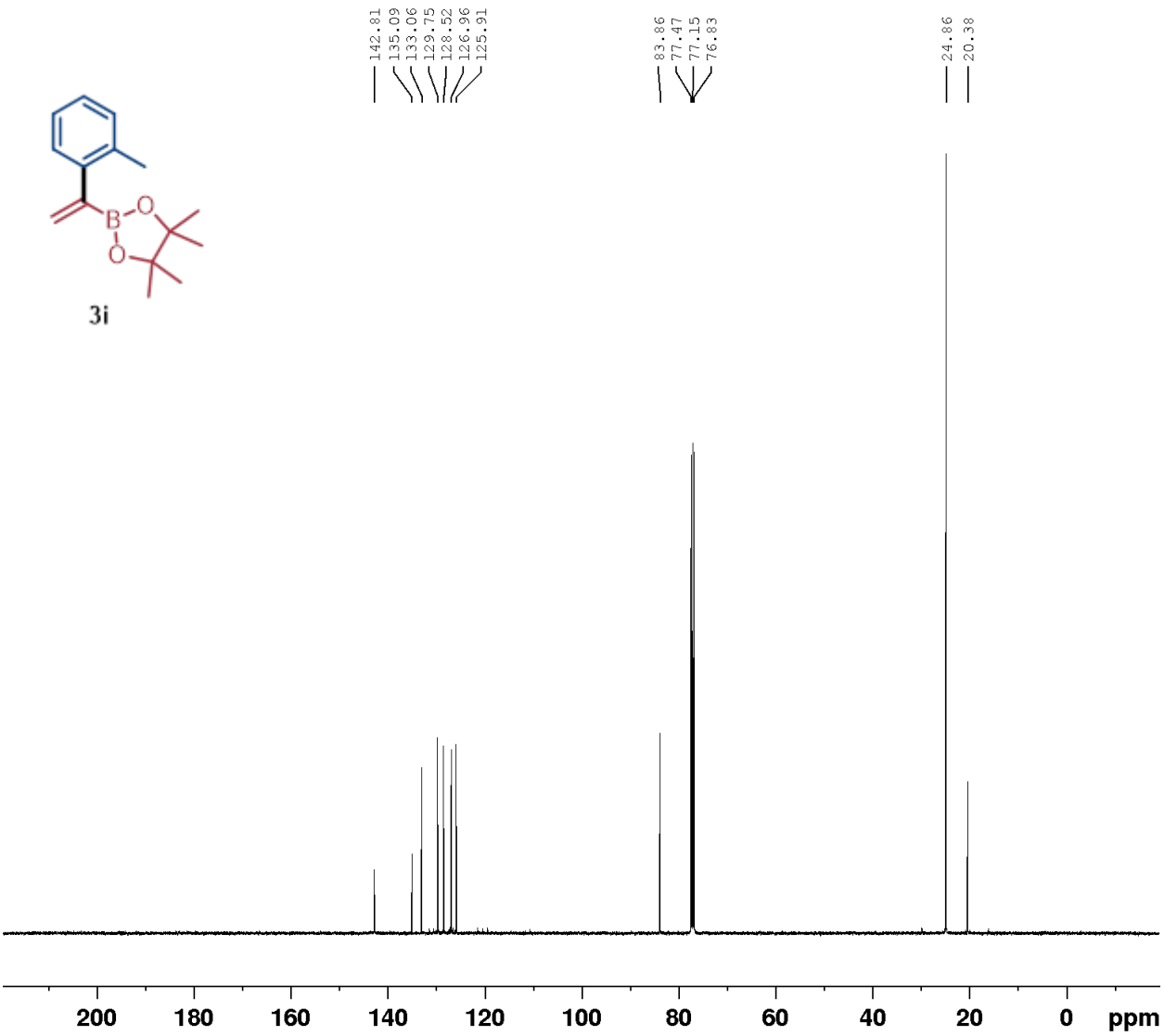
4,4,5,5-tetramethyl-2-(1-(4-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3h), ^{11}B, $CDCl_3$, 96 MHz



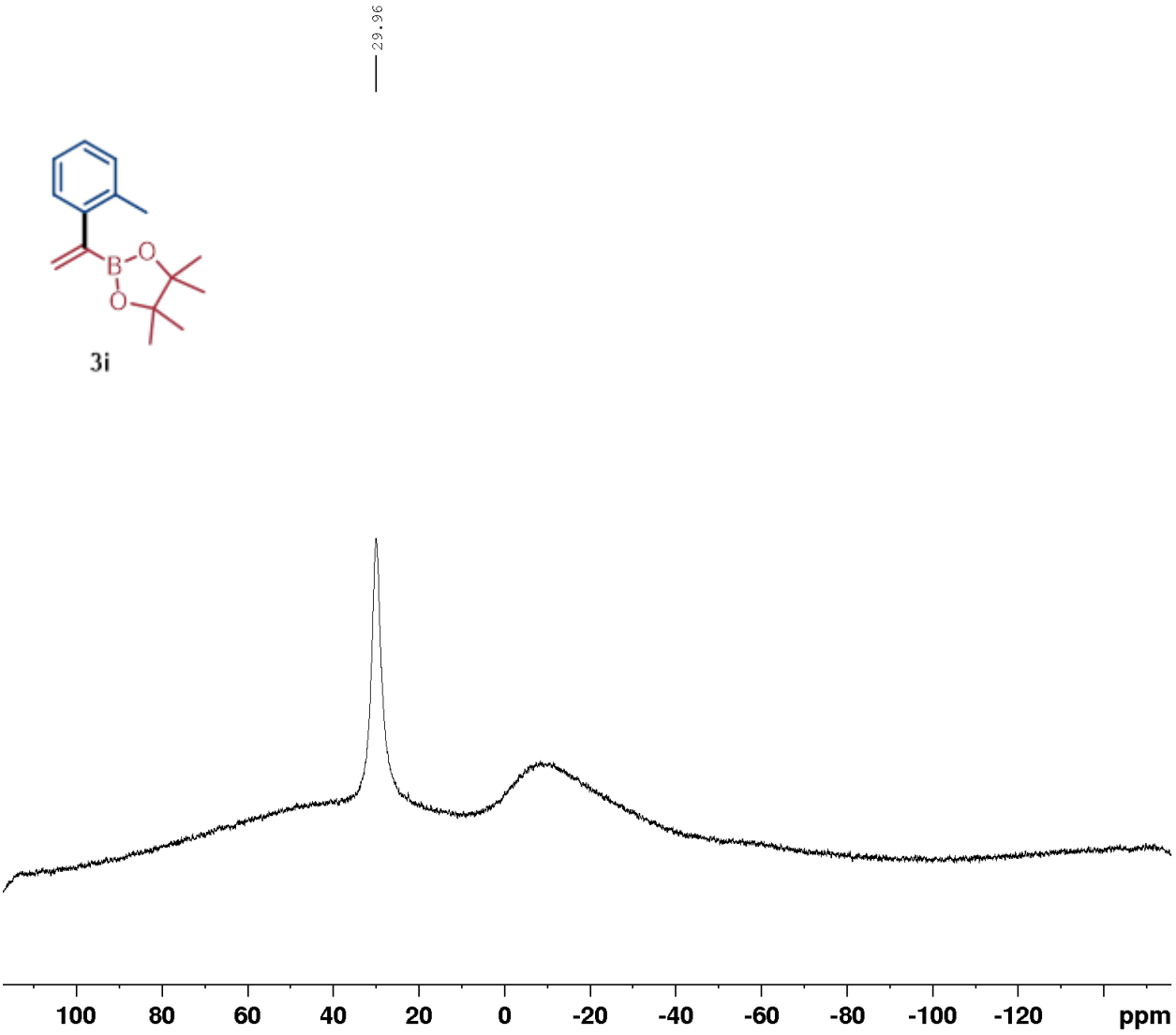
4,4,5,5-tetramethyl-2-(1-(o-tolyl)vinyl)-1,3,2-dioxaborolane (3i), ^{1}H, $CDCl_3$, 400 MHz



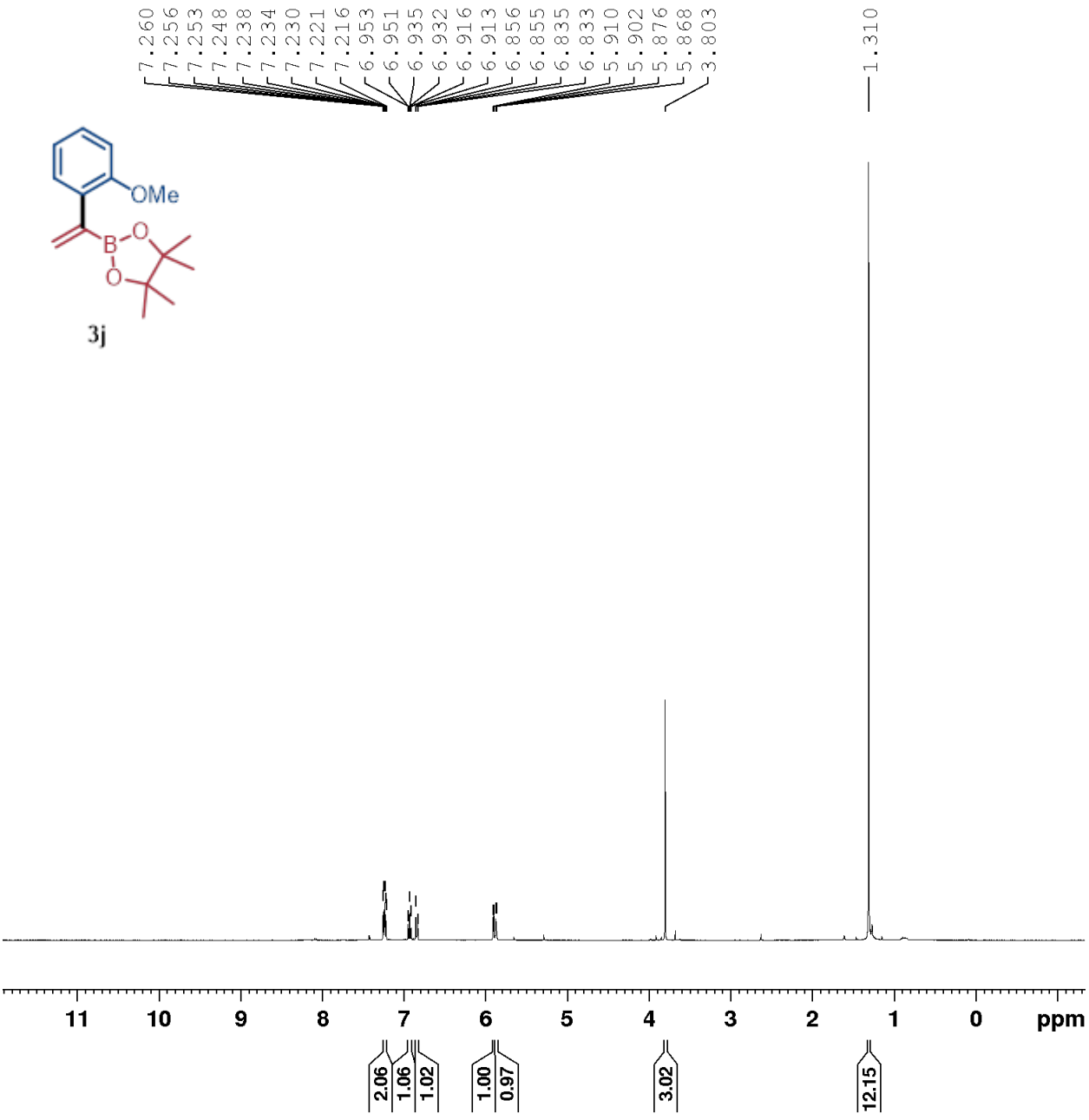
4,4,5,5-tetramethyl-2-(1-(o-tolyl)vinyl)-1,3,2-dioxaborolane (3i), ^{13}C, $CDCl_3$, 101 MHz



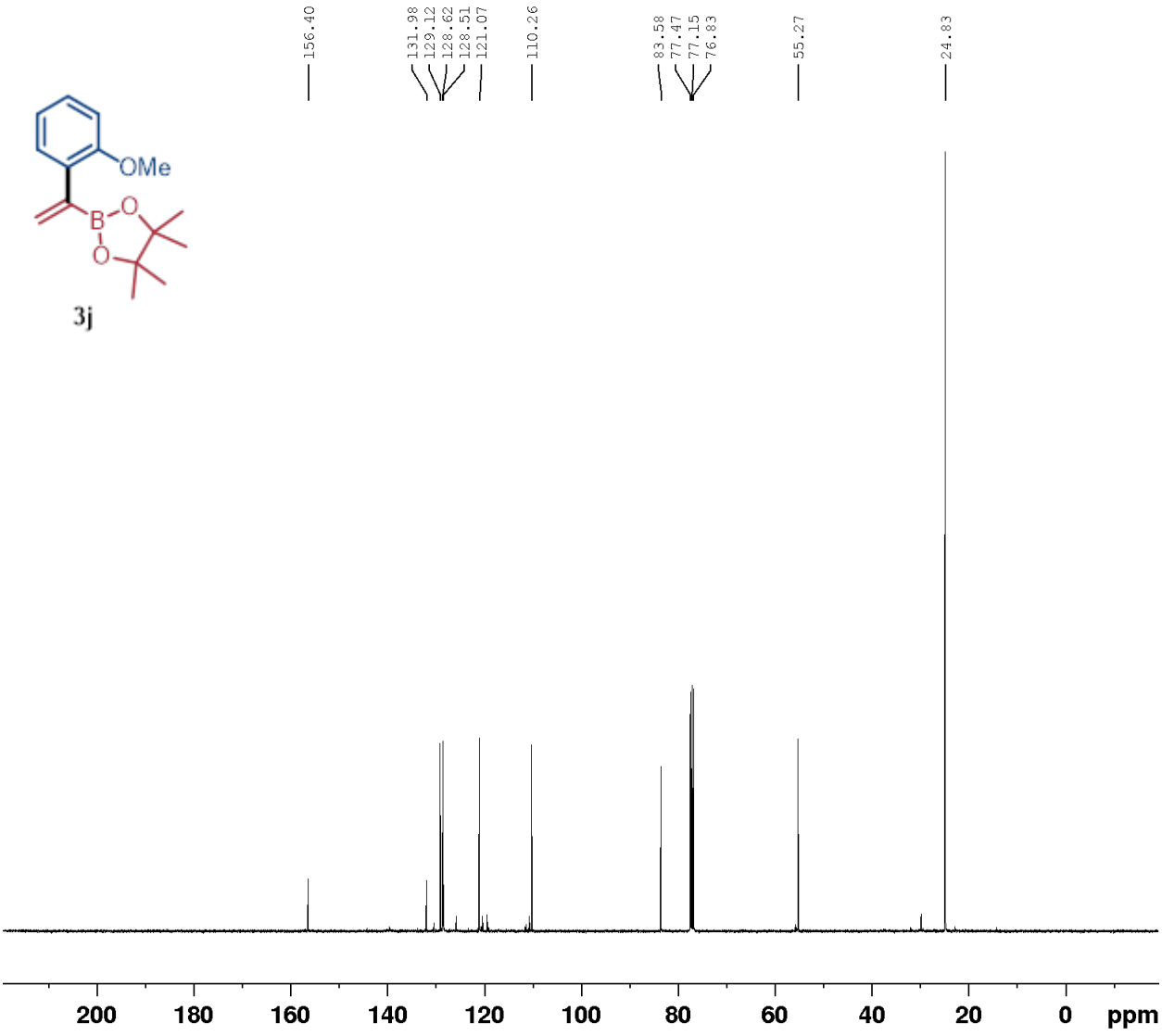
4,4,5,5-tetramethyl-2-(1-(o-tolyl)vinyl)-1,3,2-dioxaborolane (3i), ^{11}B, $CDCl_3$, 96 MHz



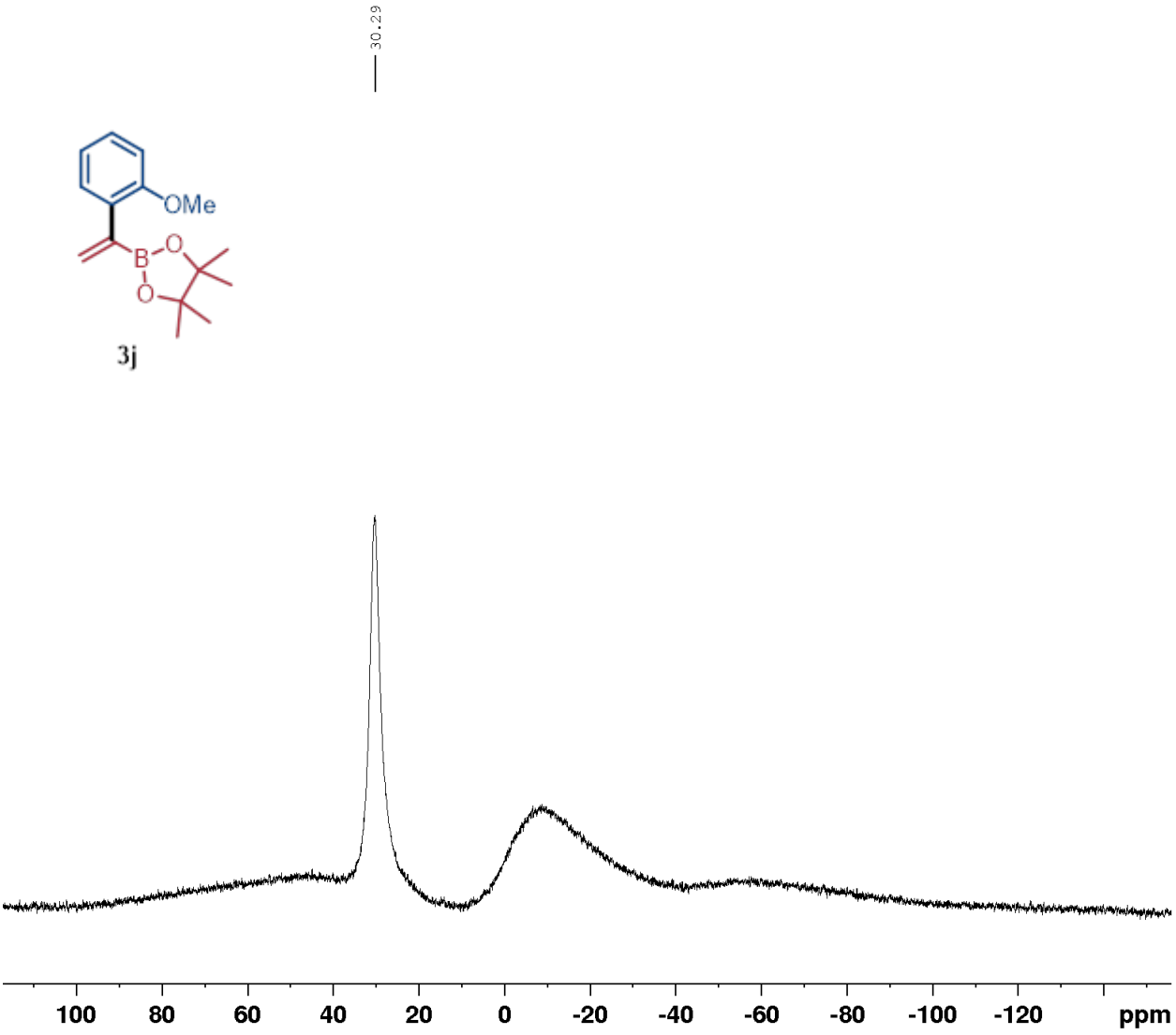
4,4,5,5-tetramethyl-2-(1-(2-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3j), ^{1}H, $CDCl_3$, 400 MHz



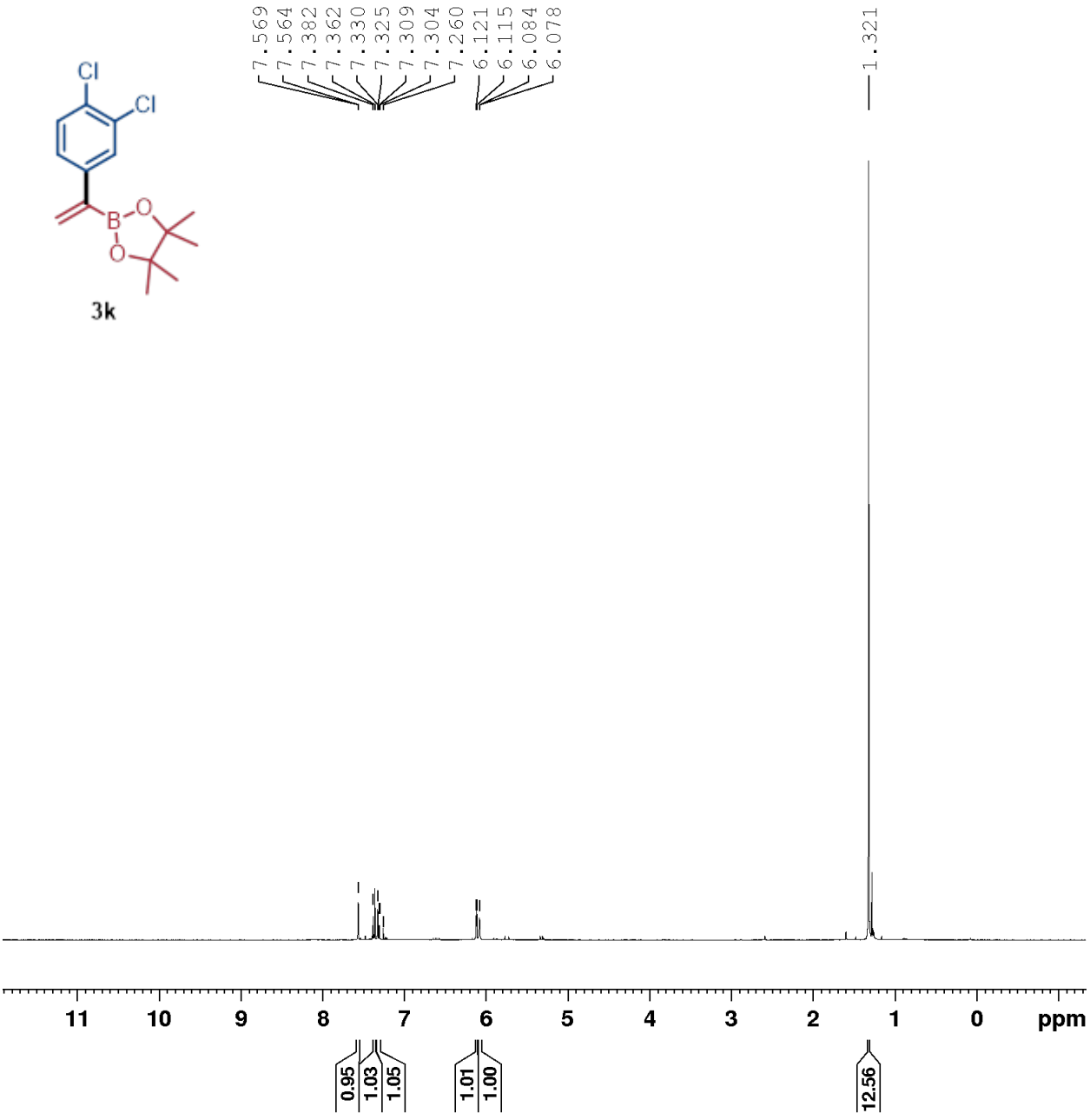
4,4,5,5-tetramethyl-2-(1-(2-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3j), ^{13}C, $CDCl_3$, 101 MHz



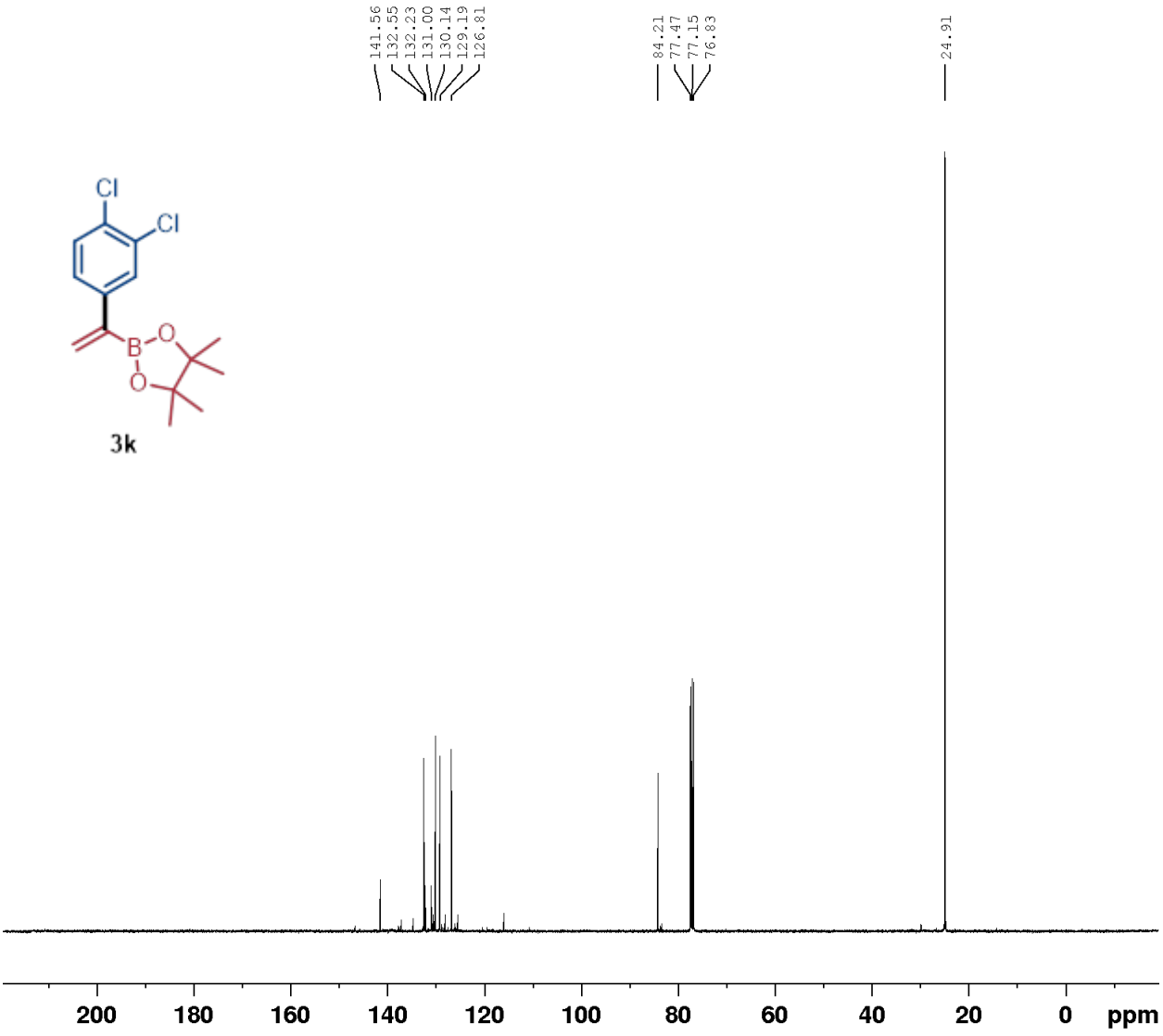
4,4,5,5-tetramethyl-2-(1-(2-methoxyphenyl)vinyl)-1,3,2-dioxaborolane (3j), ^{11}B, $CDCl_3$, 96 MHz



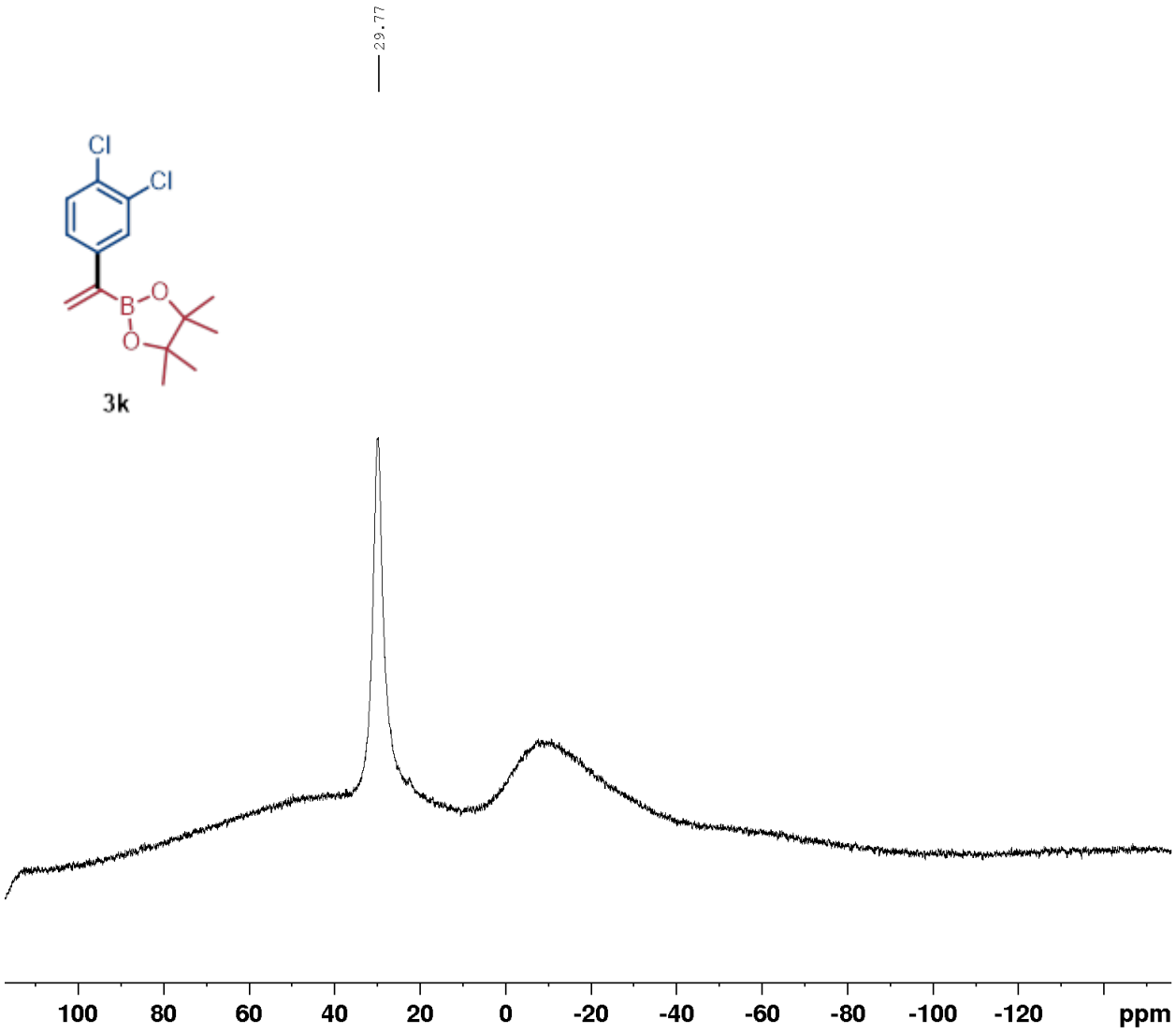
4,4,5,5-tetramethyl-2-(1-(3,4-dichlorophenyl)vinyl)-1,3,2-dioxaborolane (3k), ^{1}H, $CDCl_3$, 400 MHz



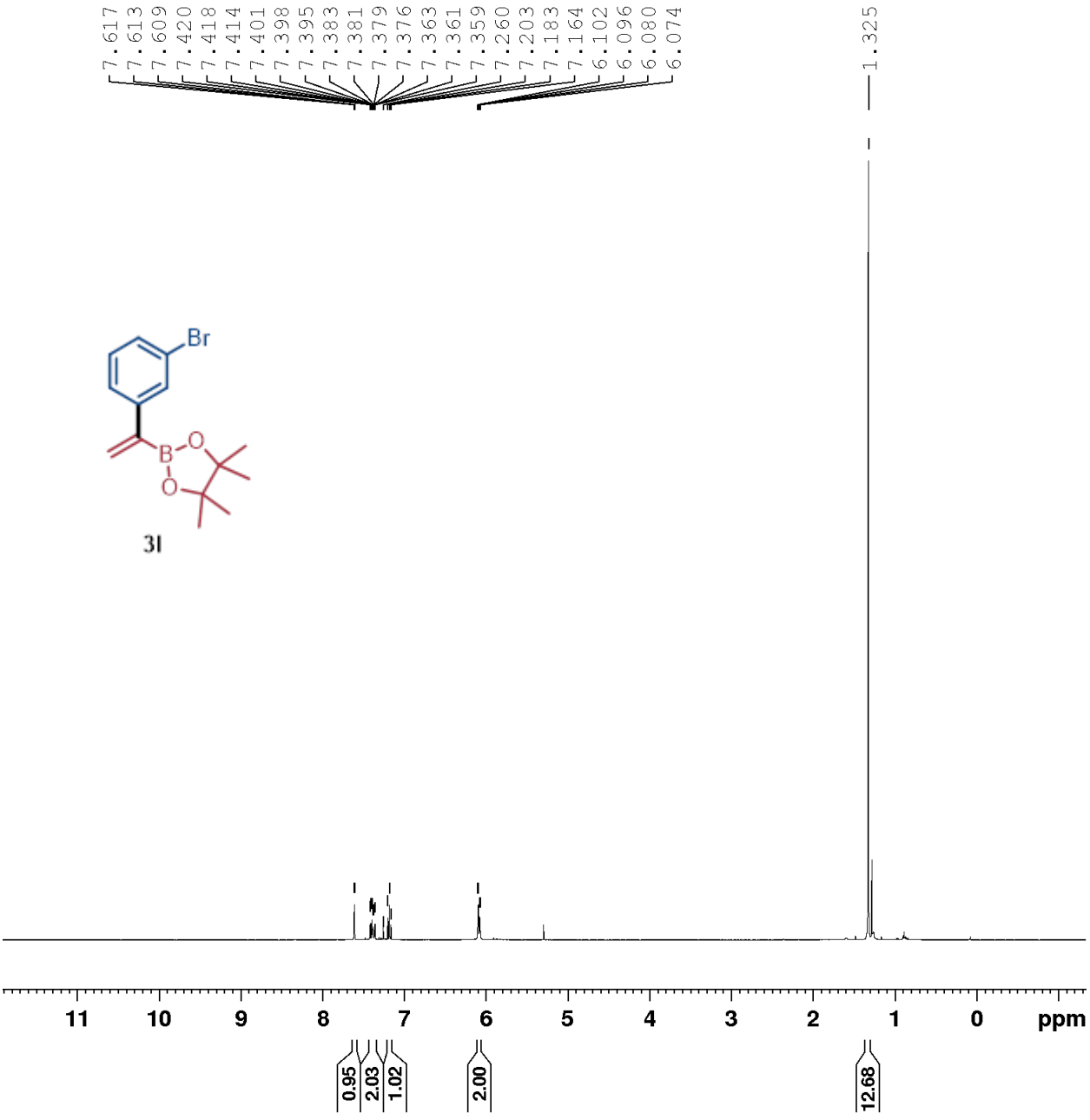
4,4,5,5-tetramethyl-2-(1-(3,4-dichlorophenyl)vinyl)-1,3,2-dioxaborolane (3k), ^{13}C, $CDCl_3$, 101 MHz



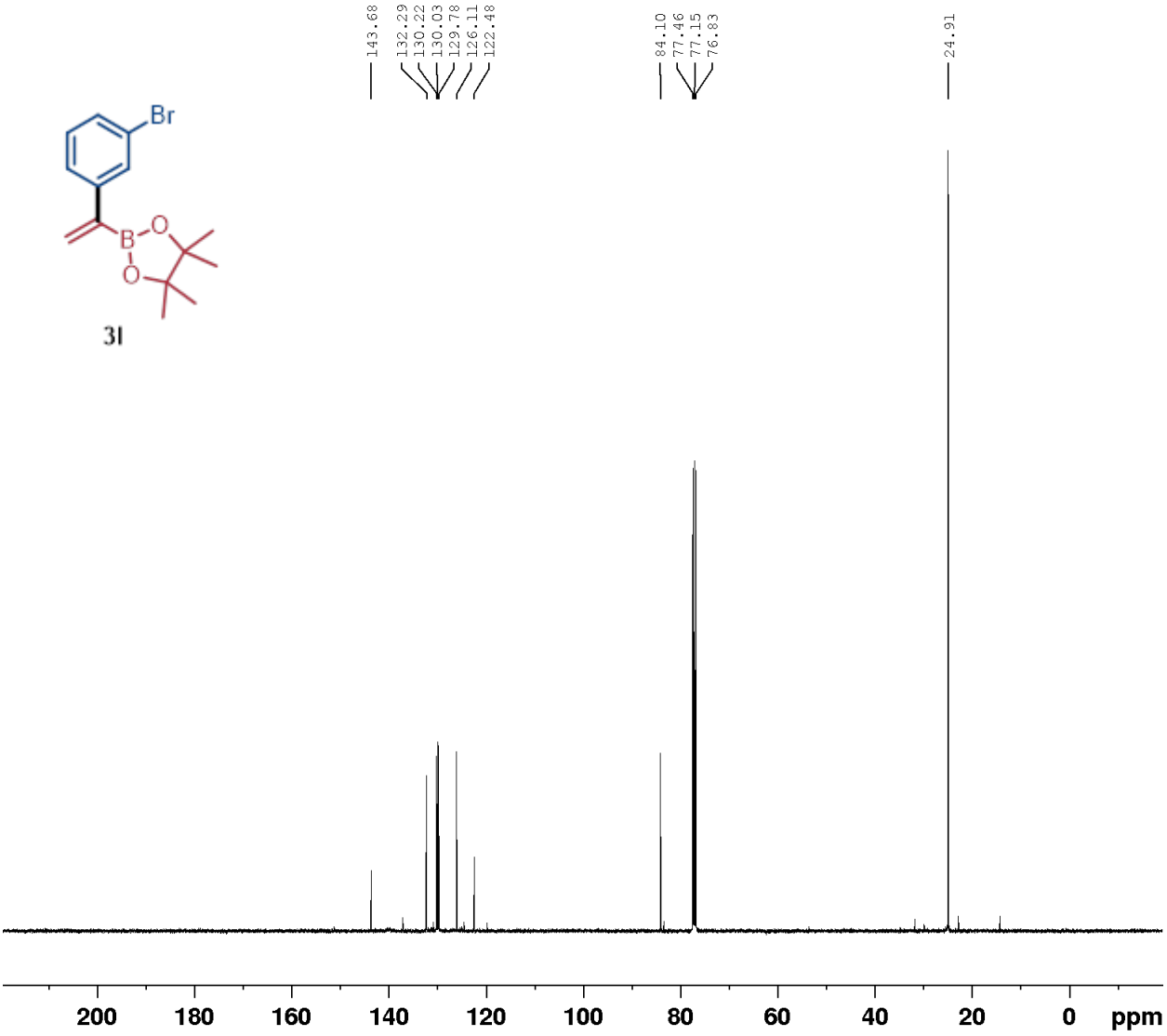
4,4,5,5-tetramethyl-2-(1-(3,4-dichlorophenyl)vinyl)-1,3,2-dioxaborolane (3k), ^{11}B, $CDCl_3$, 96 MHz



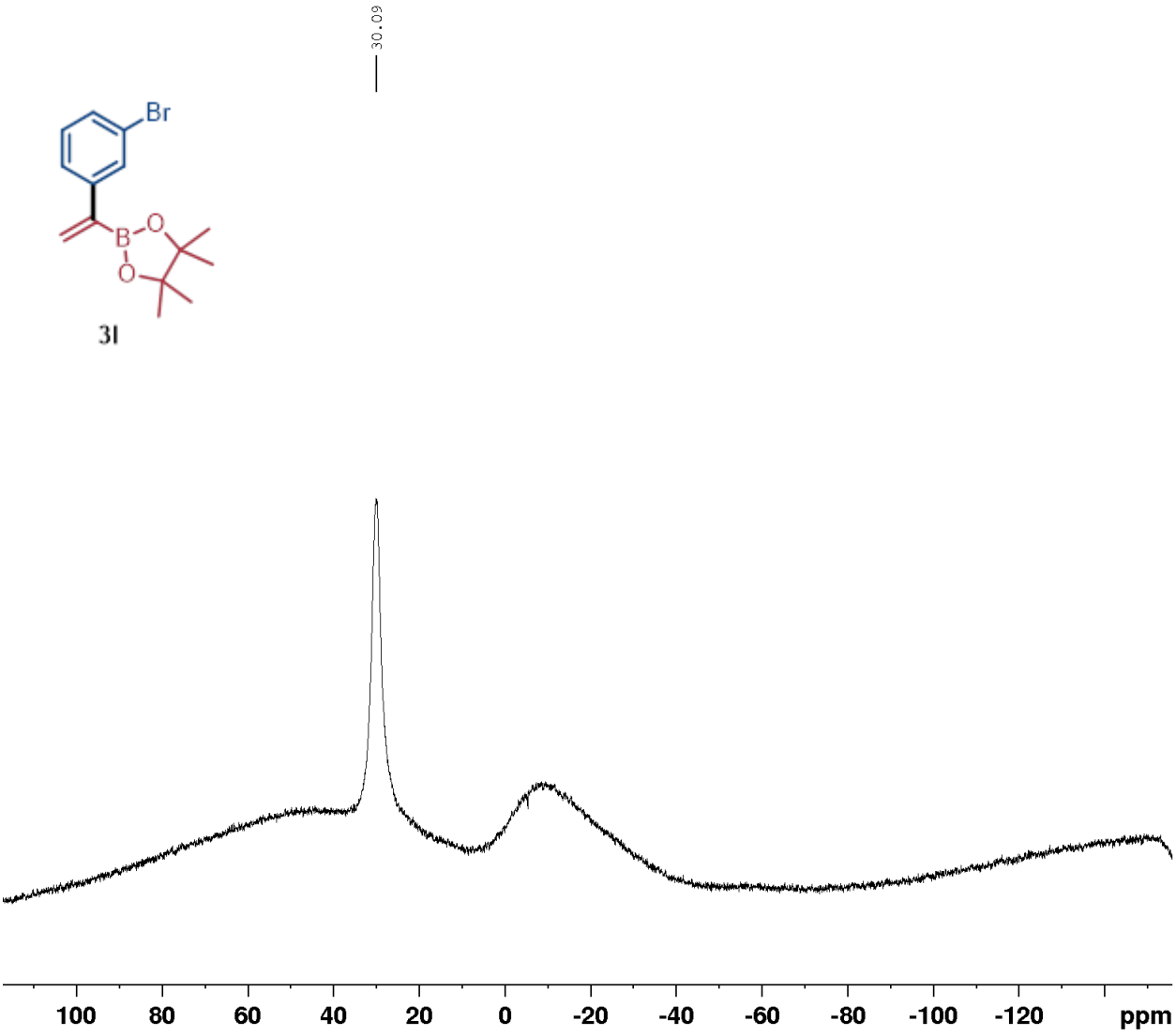
4,4,5,5-tetramethyl-2-(1-(3-bromophenyl)vinyl)-1,3,2-dioxaborolane (3l), ^{1}H, $CDCl_3$, 400 MHz



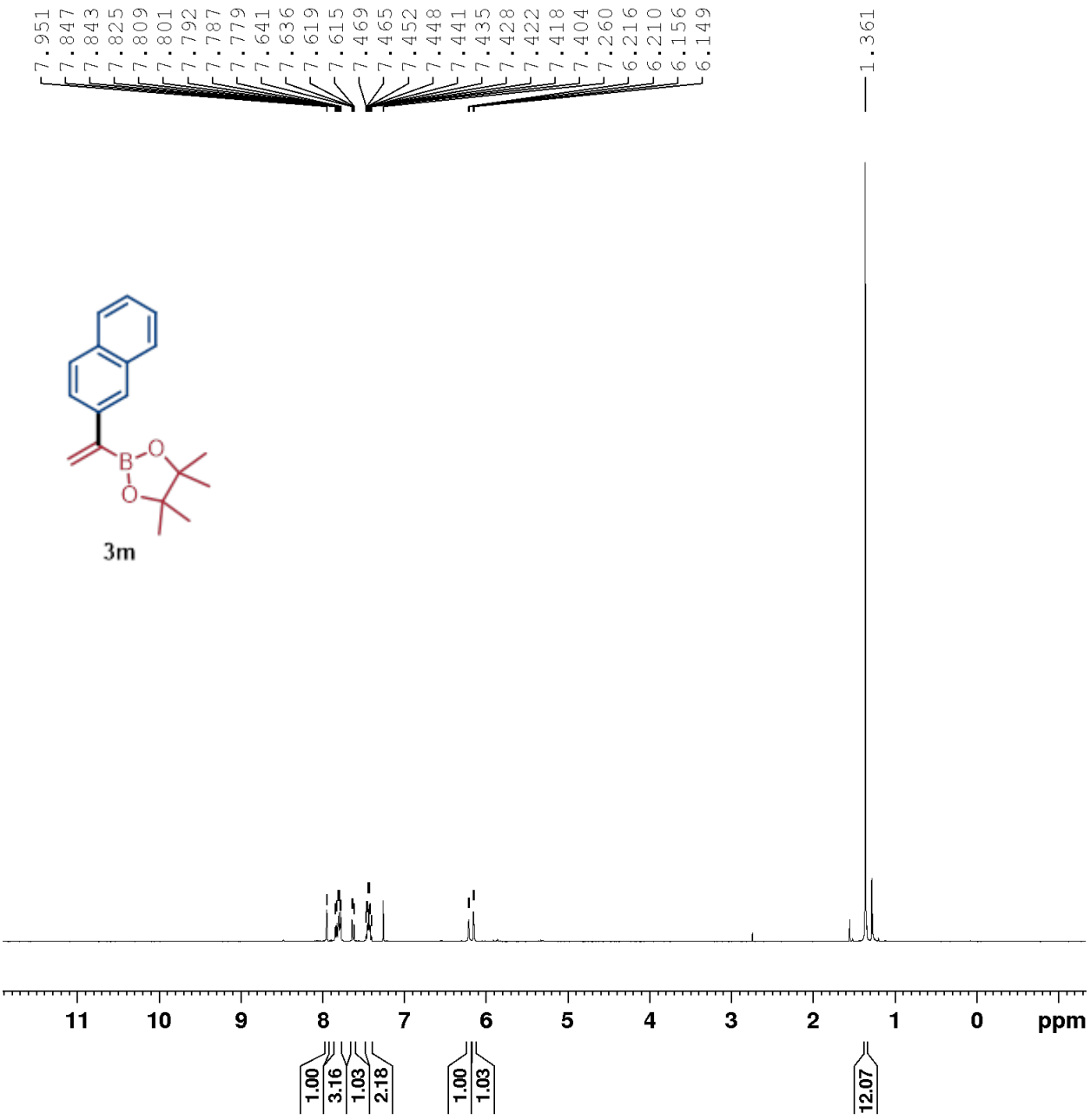
4,4,5,5-tetramethyl-2-(1-(3-bromophenyl)vinyl)-1,3,2-dioxaborolane (3l), ^{13}C, $CDCl_3$, 101 MHz



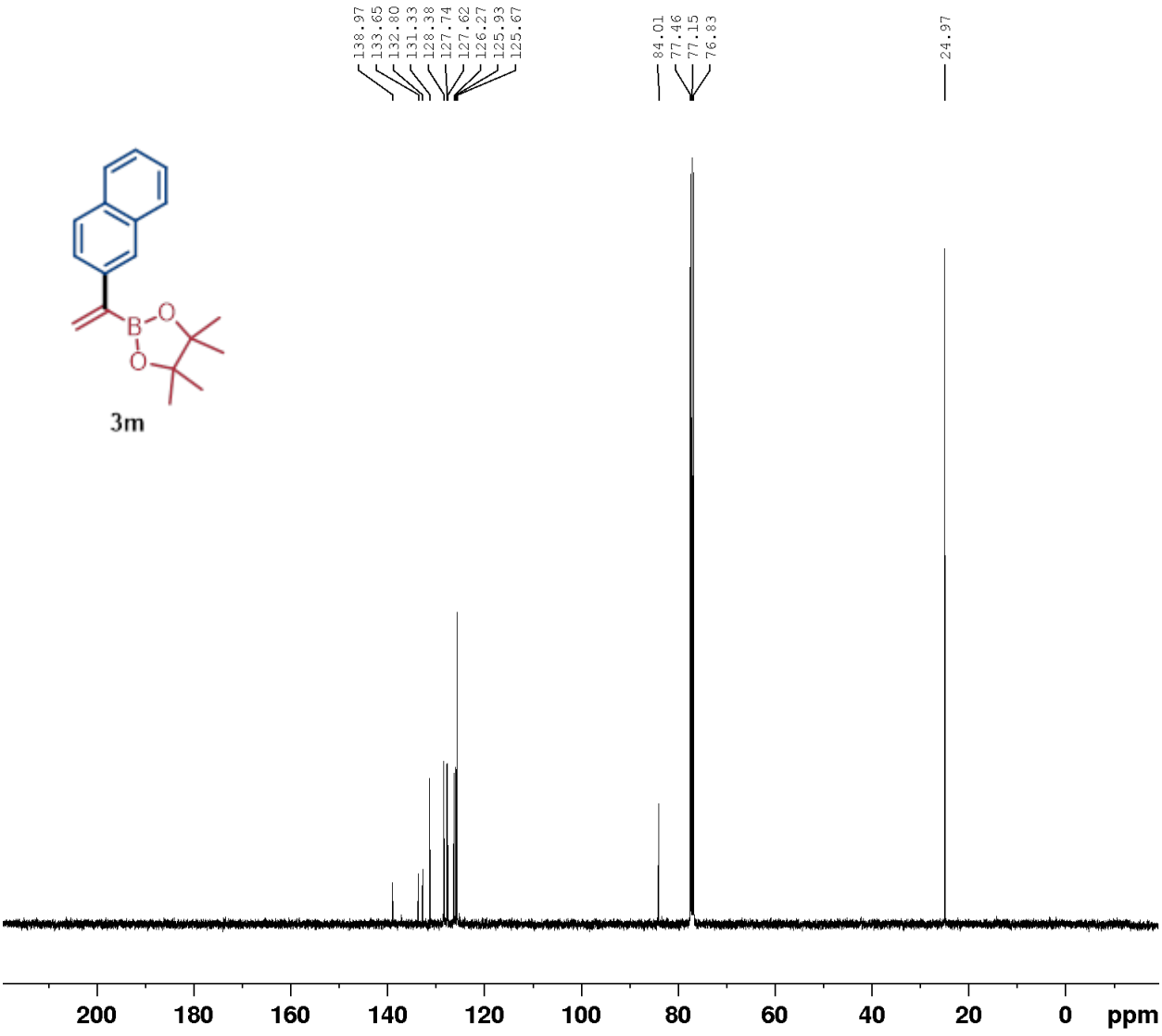
4,4,5,5-tetramethyl-2-(1-(3-bromophenyl)vinyl)-1,3,2-dioxaborolane (3l), ^{11}B, $CDCl_3$, 96 MHz



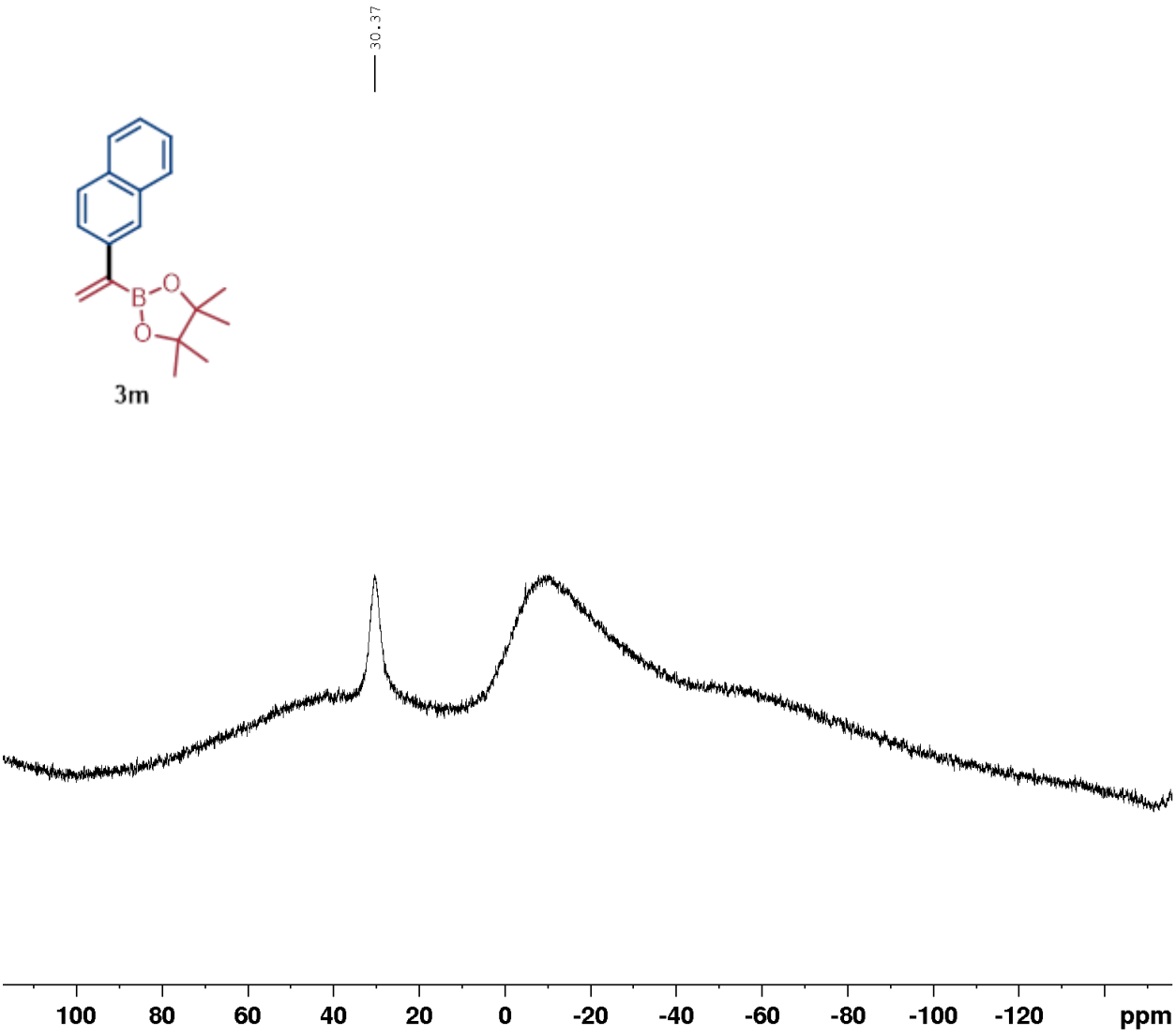
4,4,5,5-tetramethyl-2-(1-(naphthalen-2-yl)vinyl)-1,3,2-dioxaborolane (3m), ^{1}H, $CDCl_3$, 400 MHz



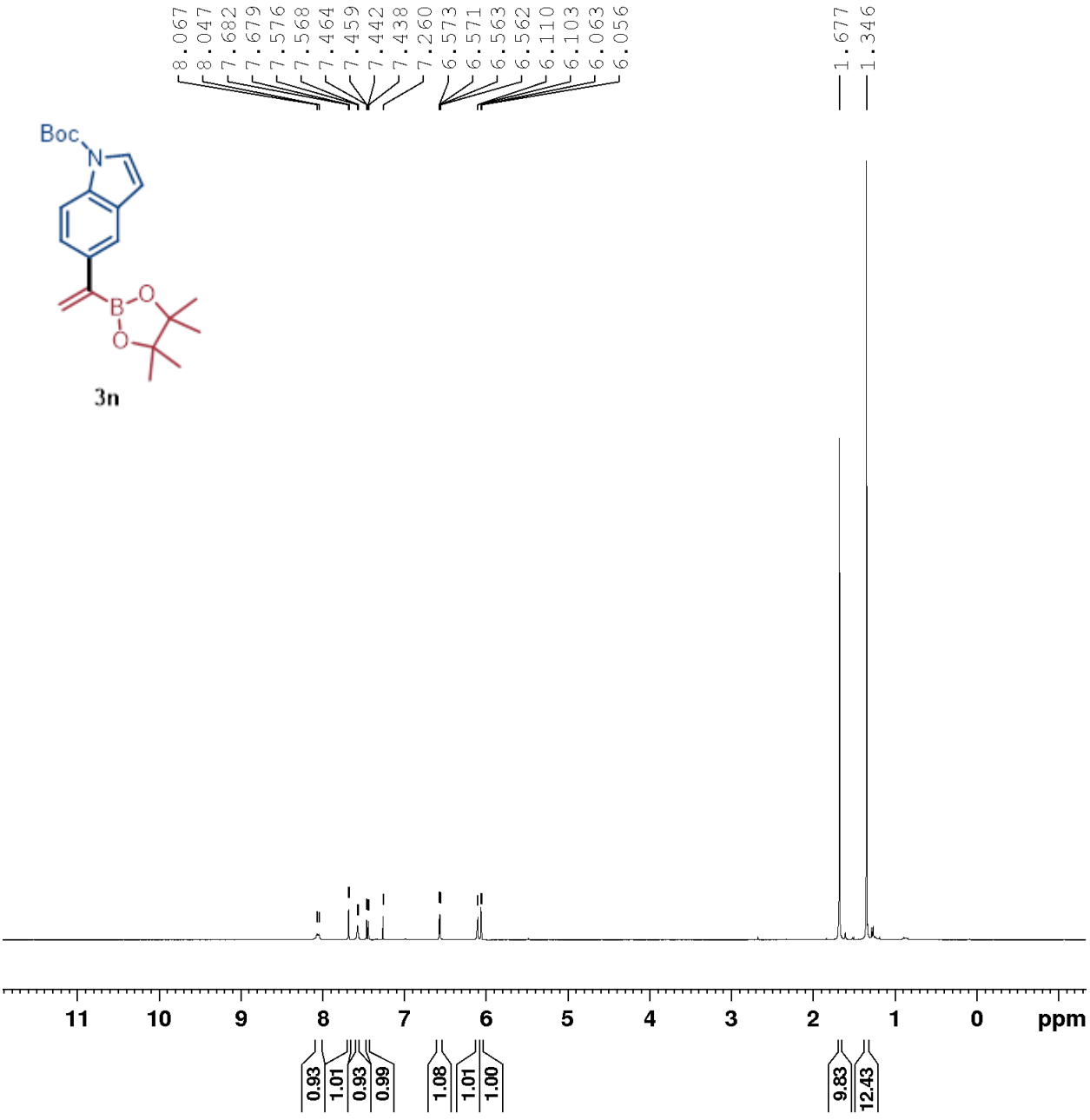
4,4,5,5-tetramethyl-2-(1-(naphthalen-2-yl)vinyl)-1,3,2-dioxaborolane (3m), ^{13}C, $CDCl_3$, 101 MHz



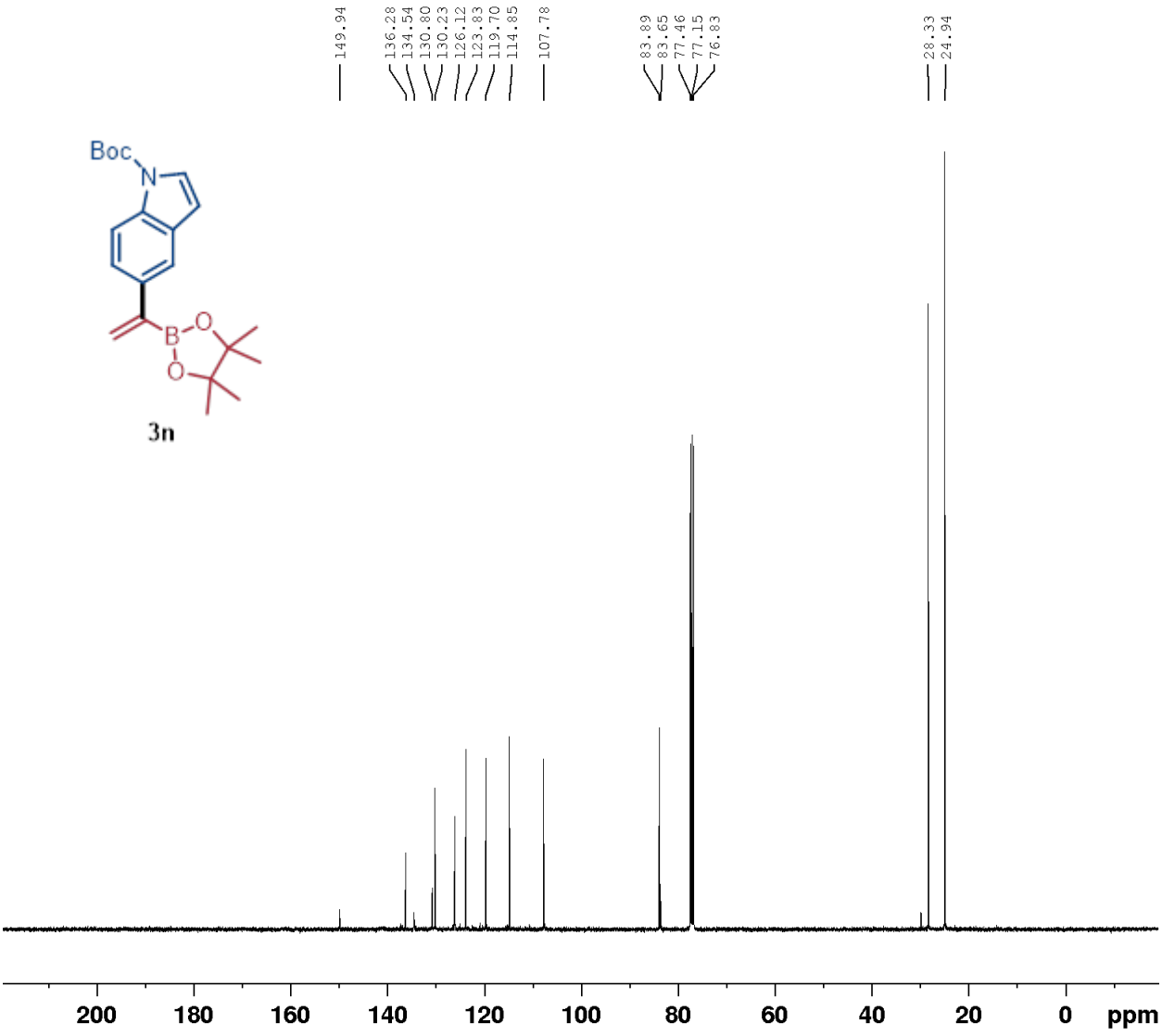
4,4,5,5-tetramethyl-2-(1-(naphthalen-2-yl)vinyl)-1,3,2-dioxaborolane (3m), ^{11}B, $CDCl_3$, 96 MHz



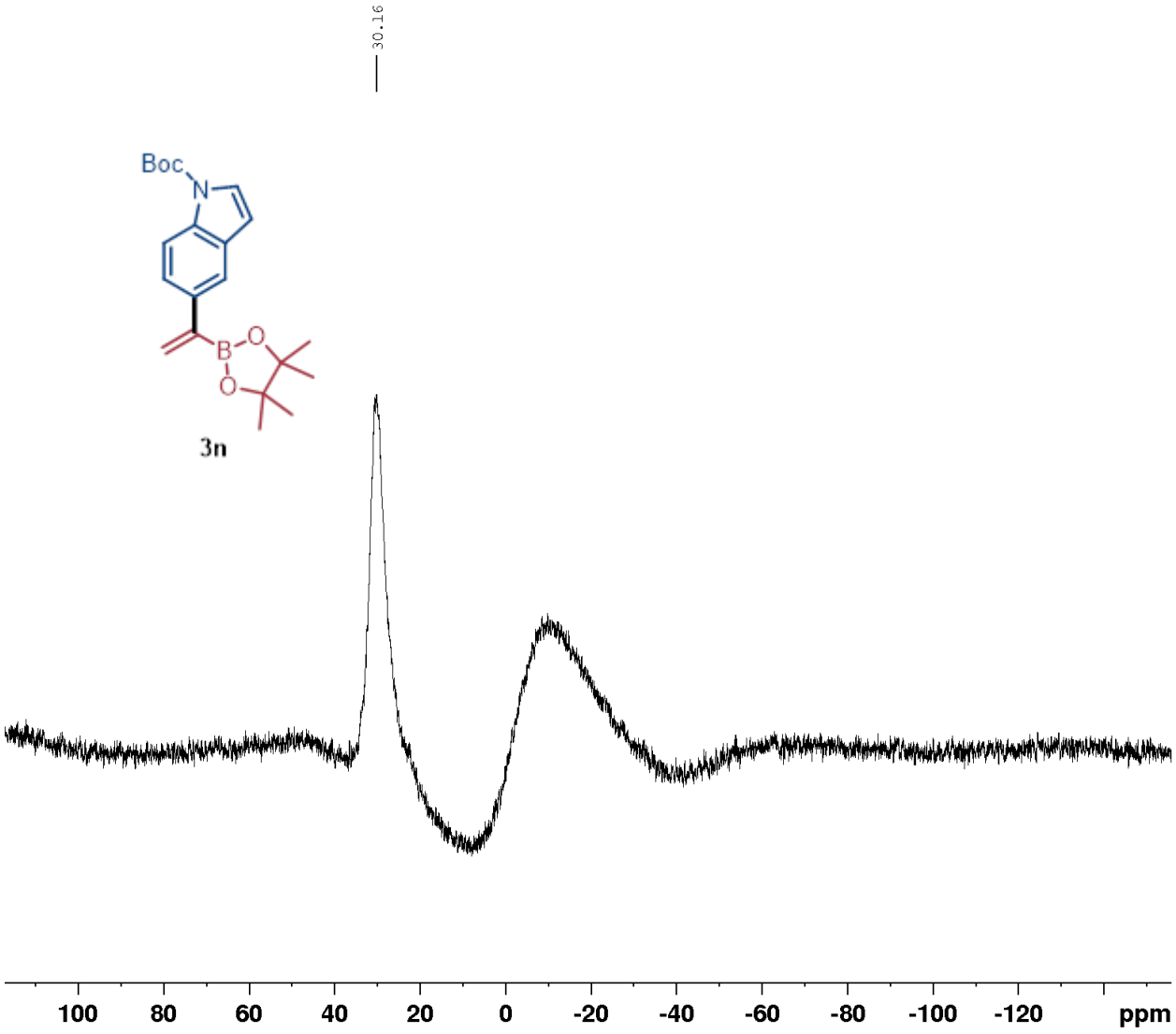
tert-butyl 5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indole-1-carboxylate (3n), ^{1}H, $CDCl_3$, 400 MHz



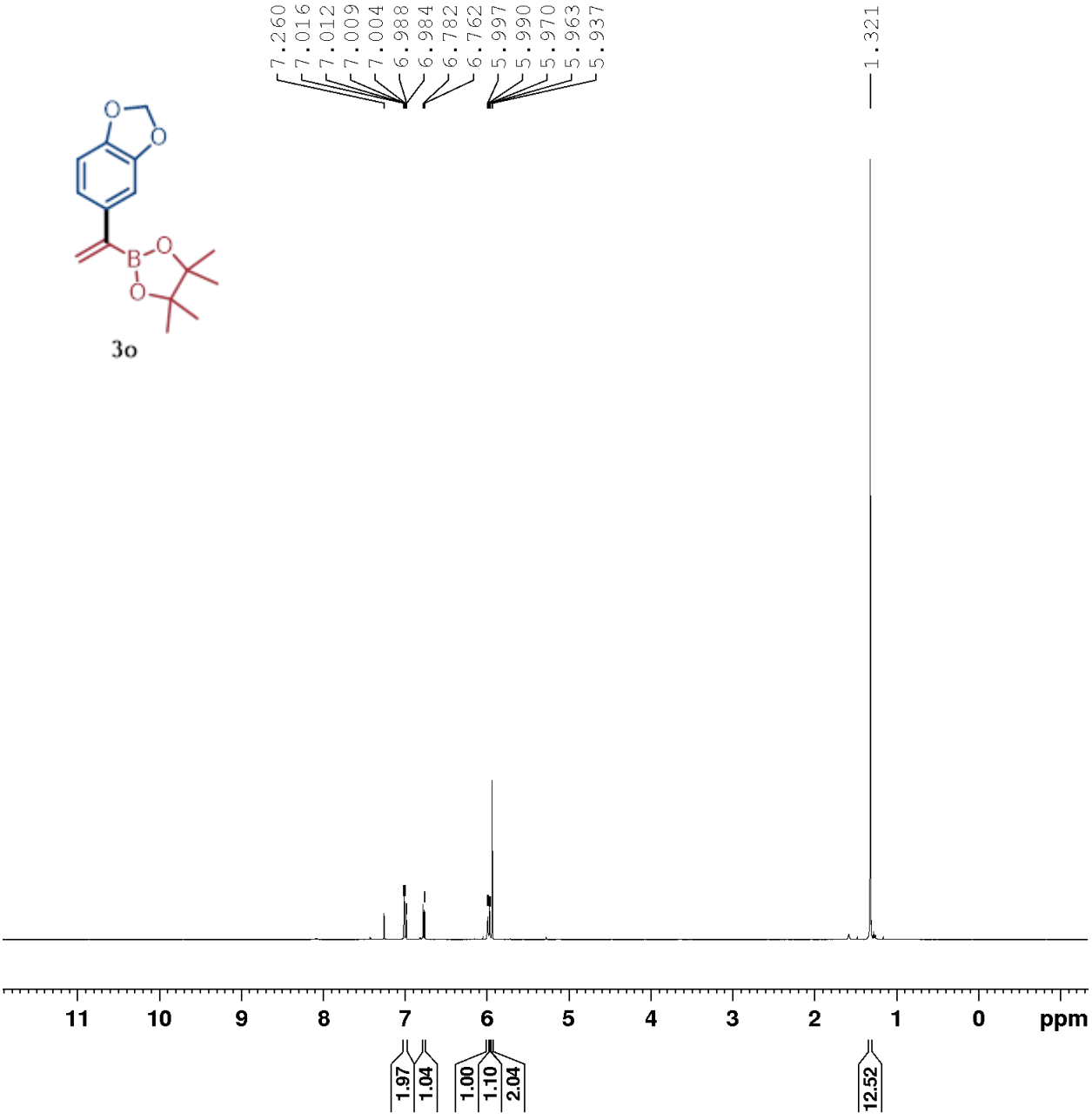
tert-butyl 5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indole-1-carboxylate (3n), ^{13}C, $CDCl_3$, 101 MHz



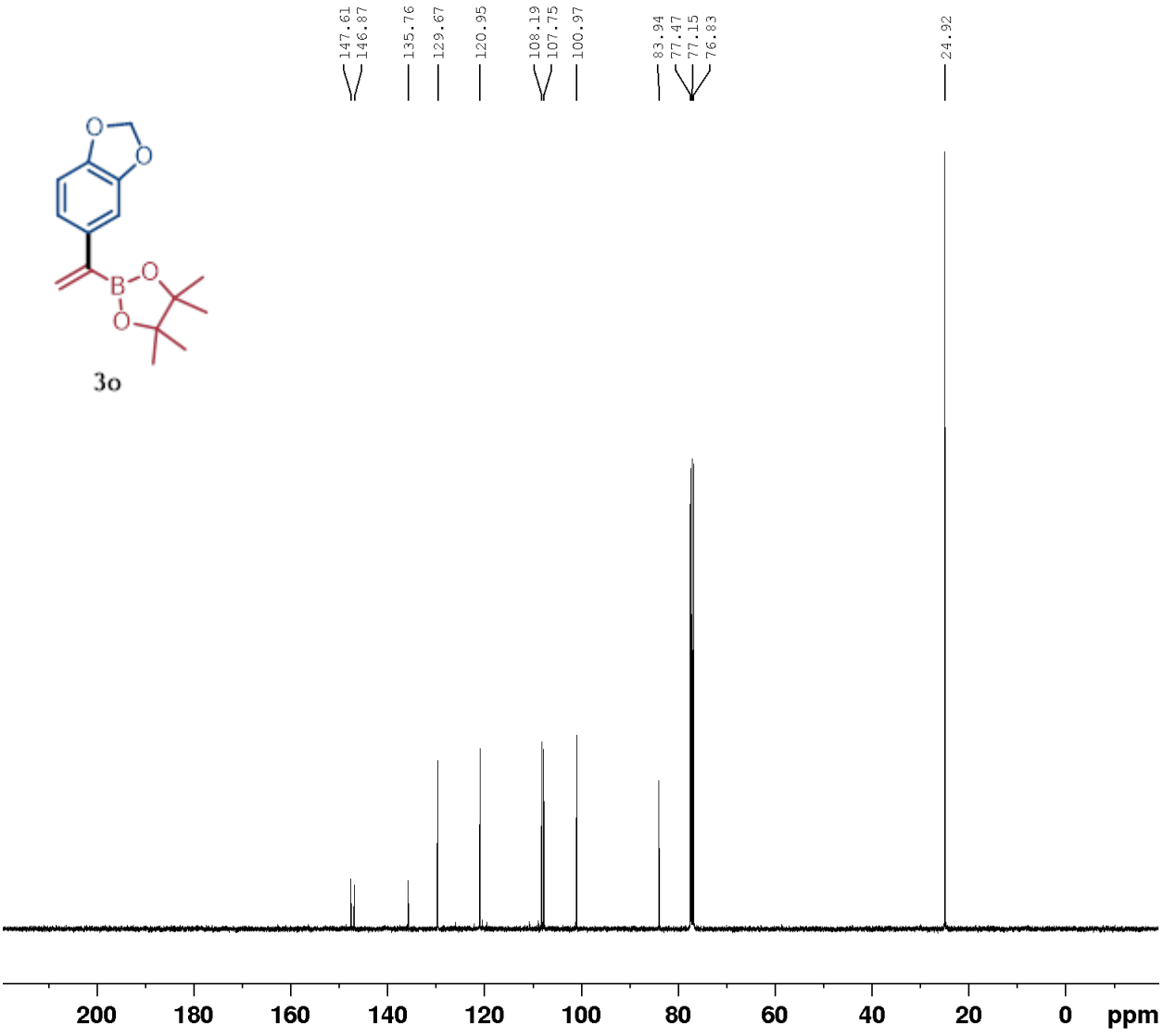
tert-butyl 5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1H-indole-1-carboxylate (3n), ^{11}B, $CDCl_3$, 96 MHz



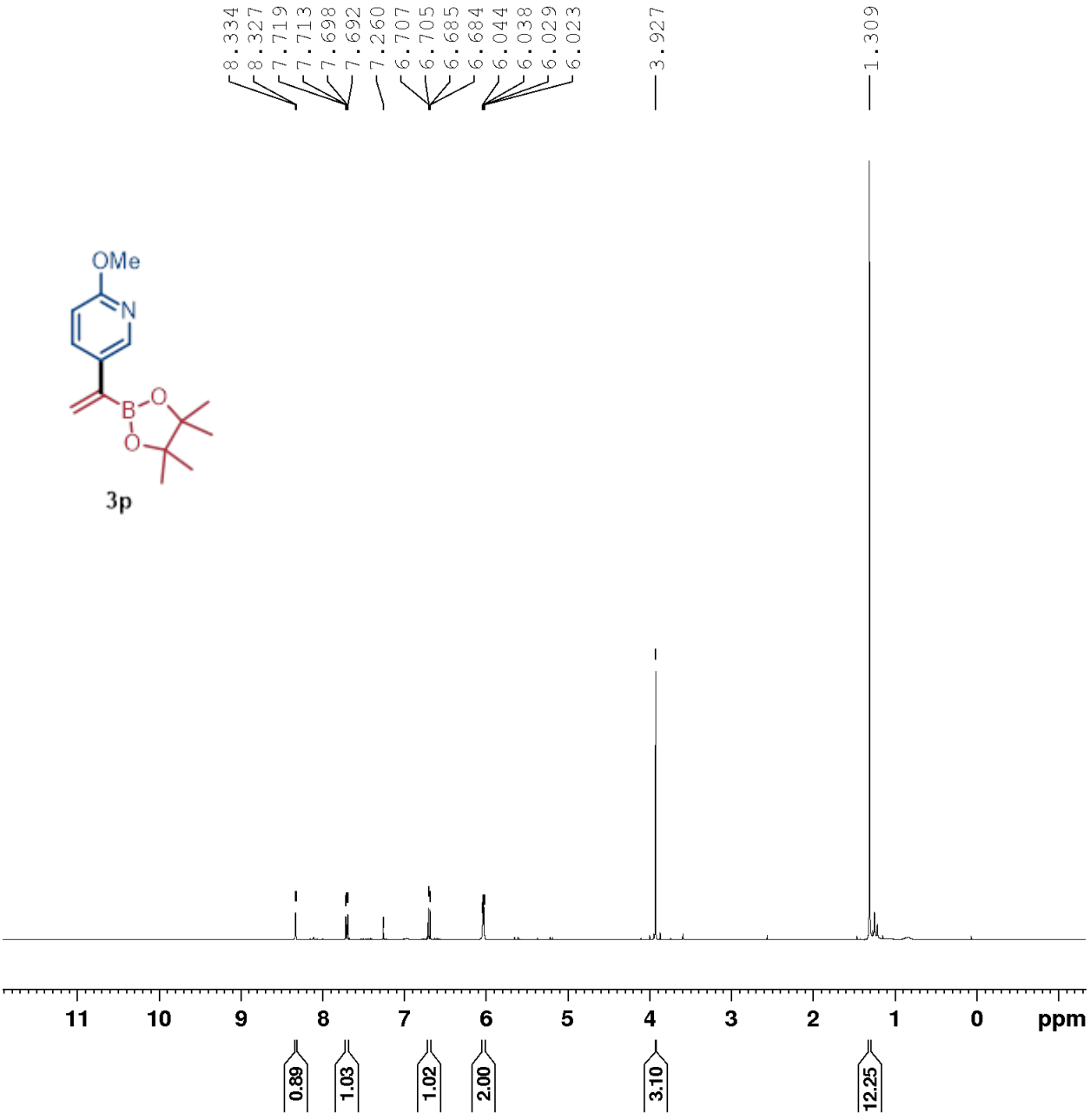
4,4,5,5-tetramethyl-2-(1-(benzo[d][1,3]dioxol-5-yl)vinyl)-1,3,2-dioxaborolane (3o), ^{1}H, $CDCl_3$, 400 MHz



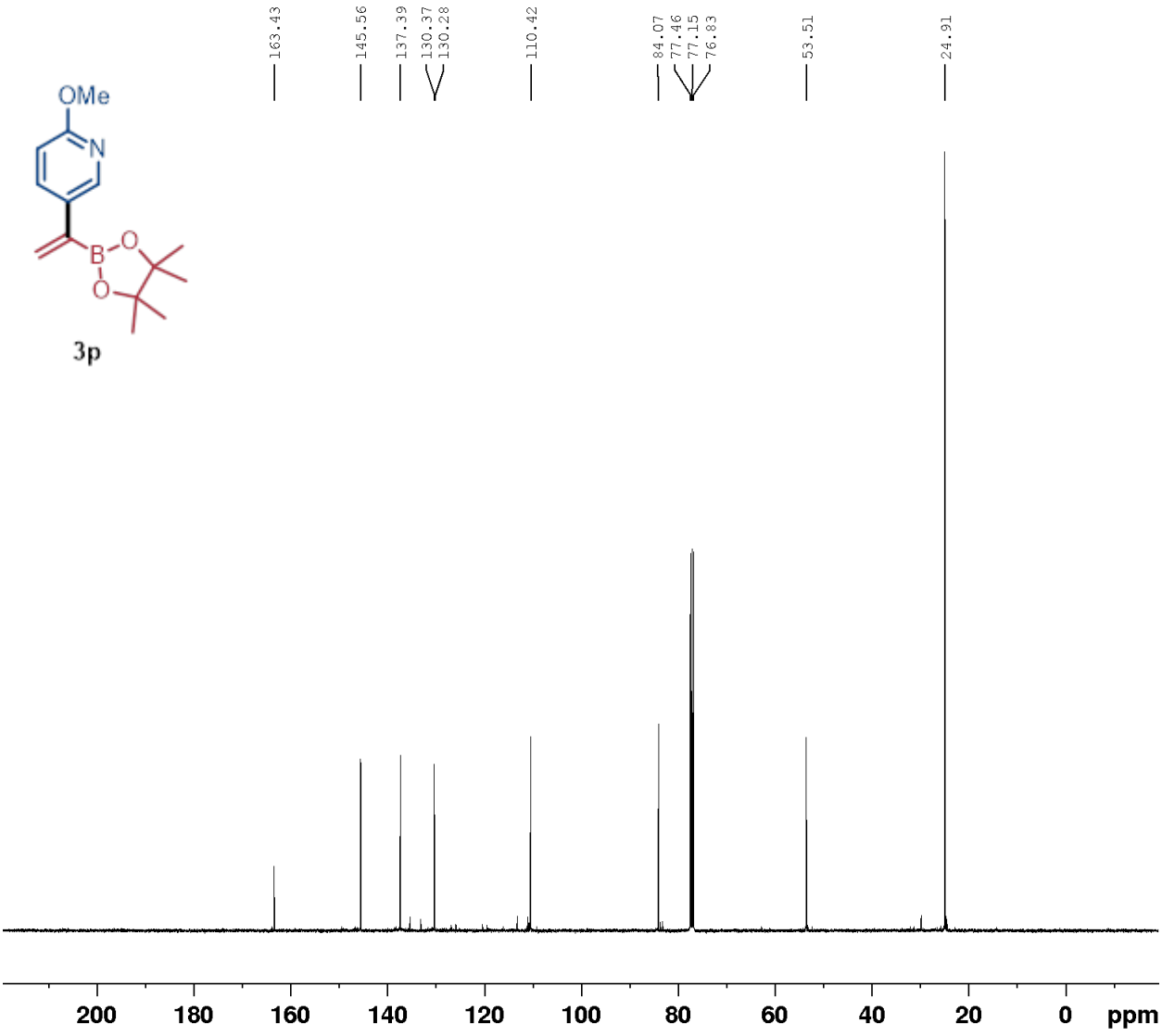
4,4,5,5-tetramethyl-2-(1-(benzo[d][1,3]dioxol-5-yl)vinyl)-1,3,2-dioxaborolane (3o), ^{13}C, $CDCl_3$, 101 MHz



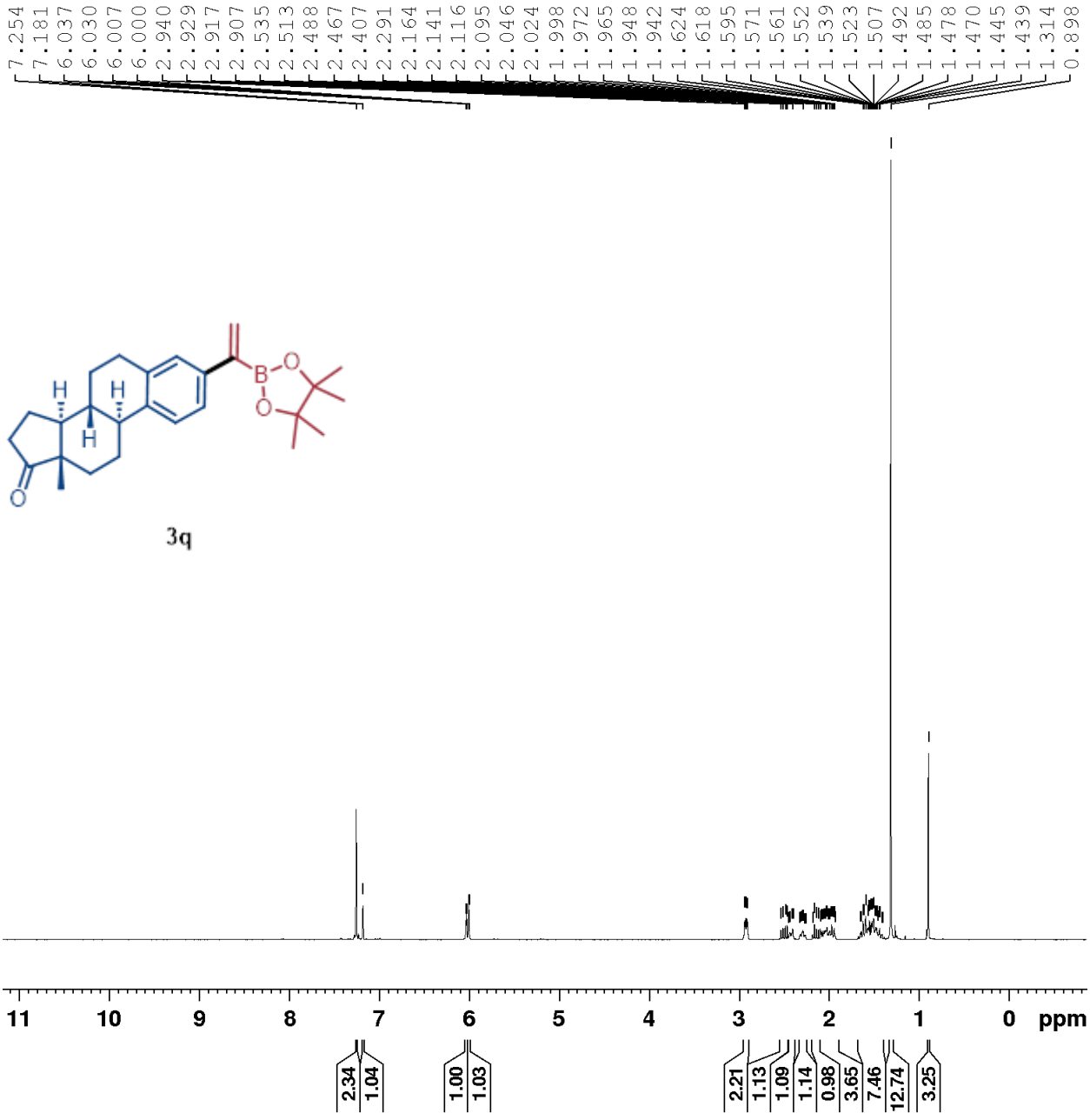
2-methoxy-5-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]pyridine (3p), ^{1}H, $CDCl_3$, 400 MHz



2-methoxy-5-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethenyl]pyridine (3p), ^{13}C, $CDCl_3$, 101 MHz

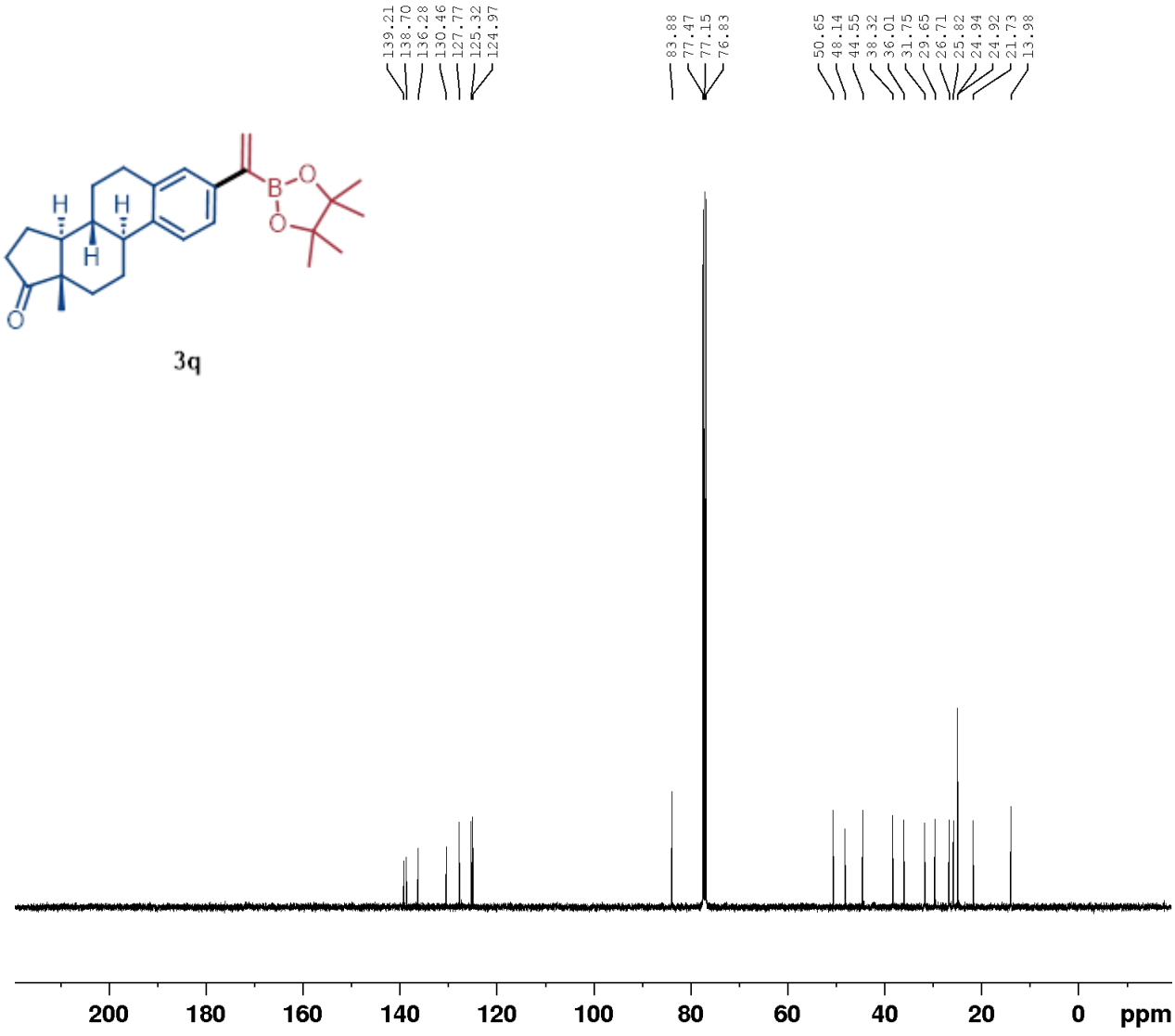


(8R,9S,13S,14S)-13-methyl-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (3q), ^{1}H, $CDCl_3$, 400 MHz

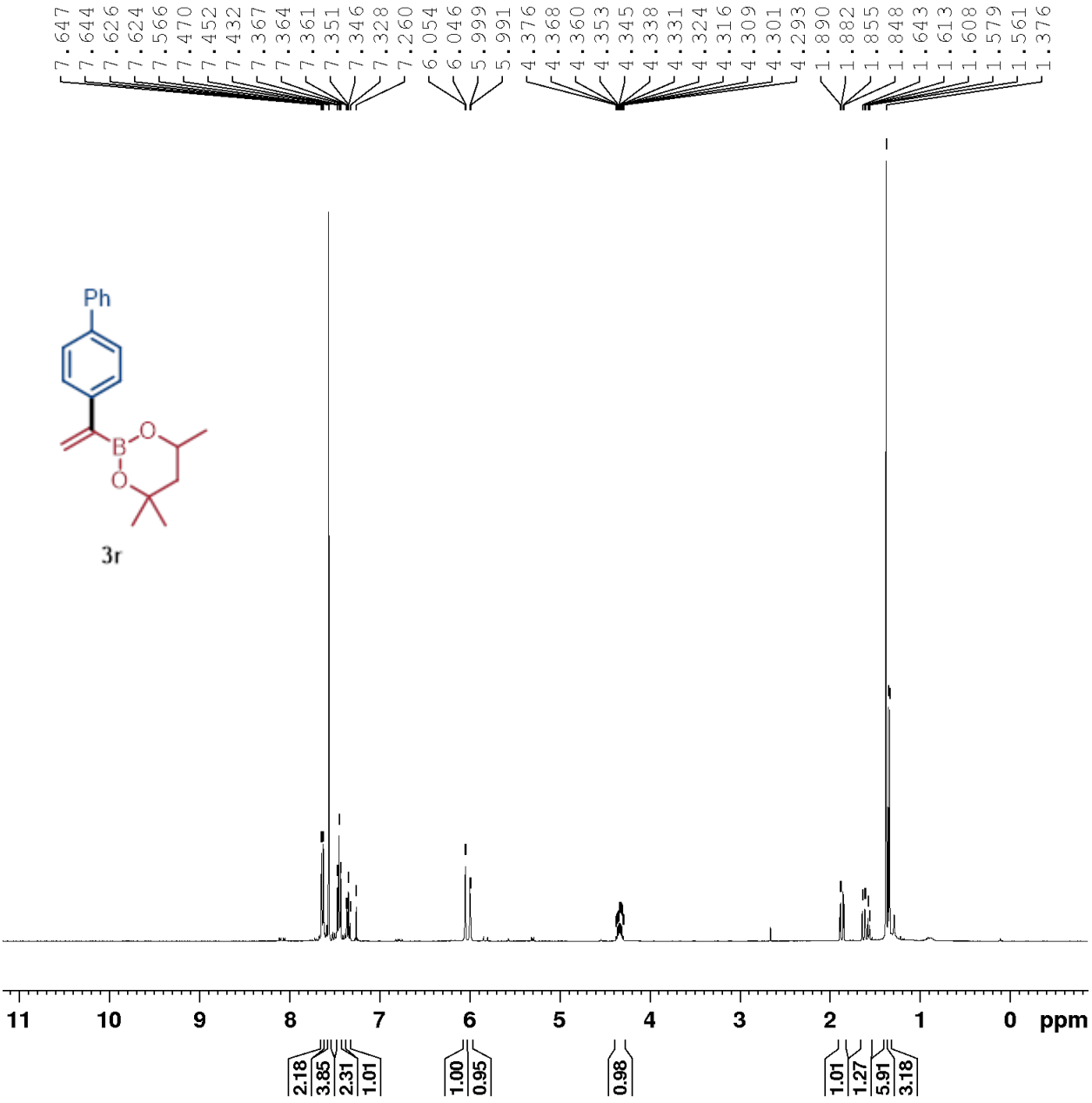


3q

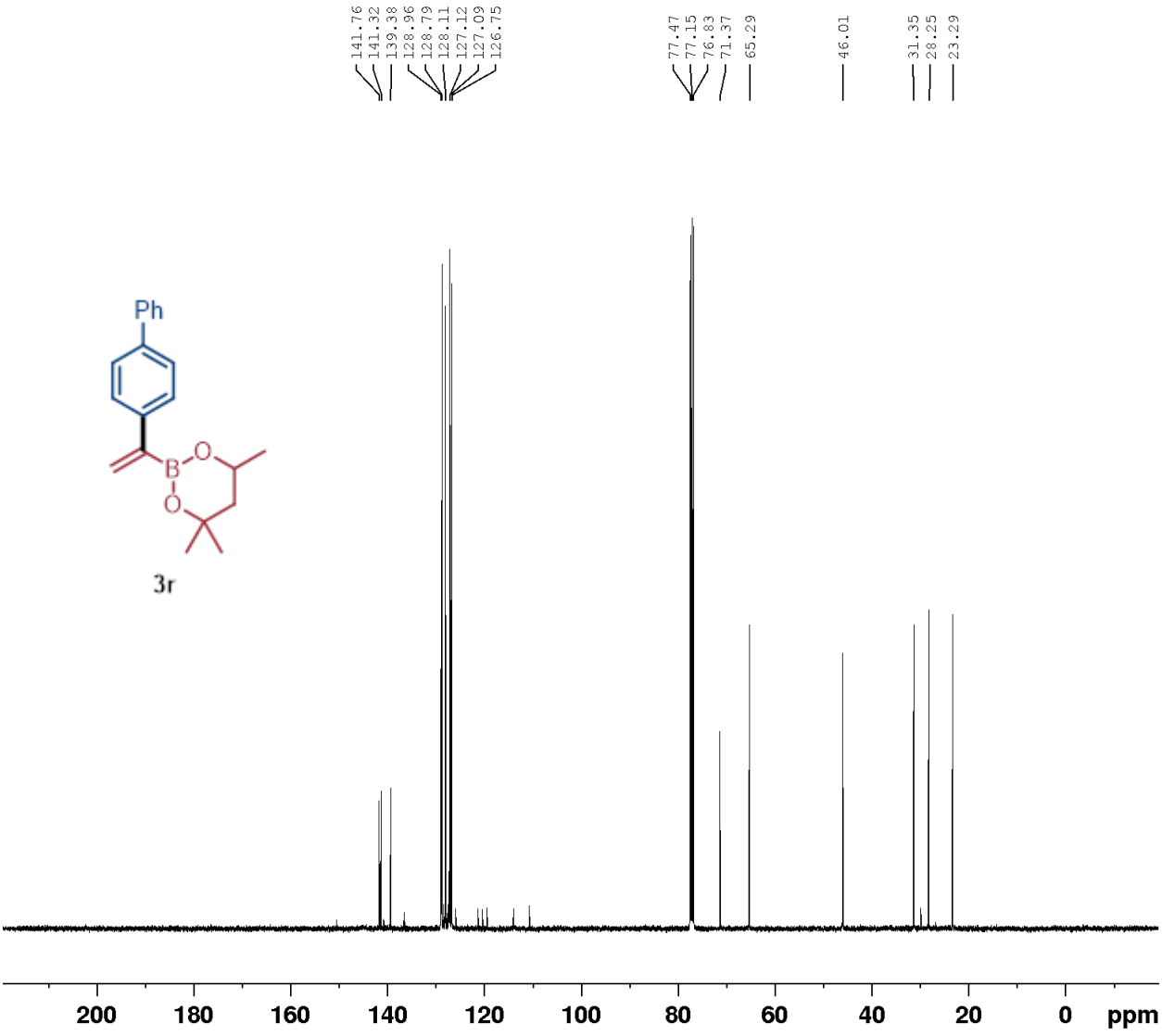
(8R,9S,13S,14S)-13-methyl-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (3q), ^{13}C, $CDCl_3$, 101 MHz



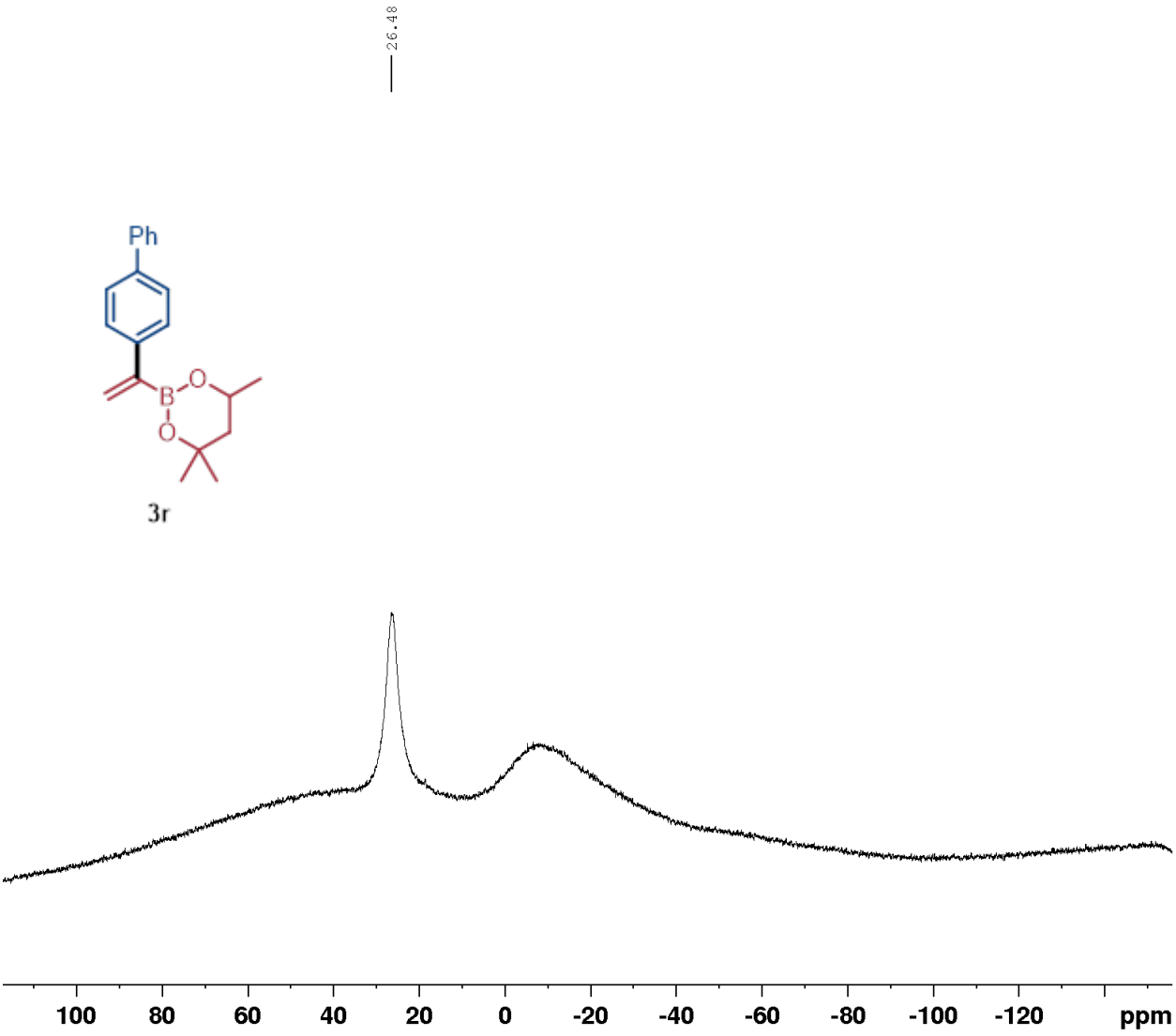
4,4,6-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborinane (3r), ^{1}H, $CDCl_3$, 400 MHz



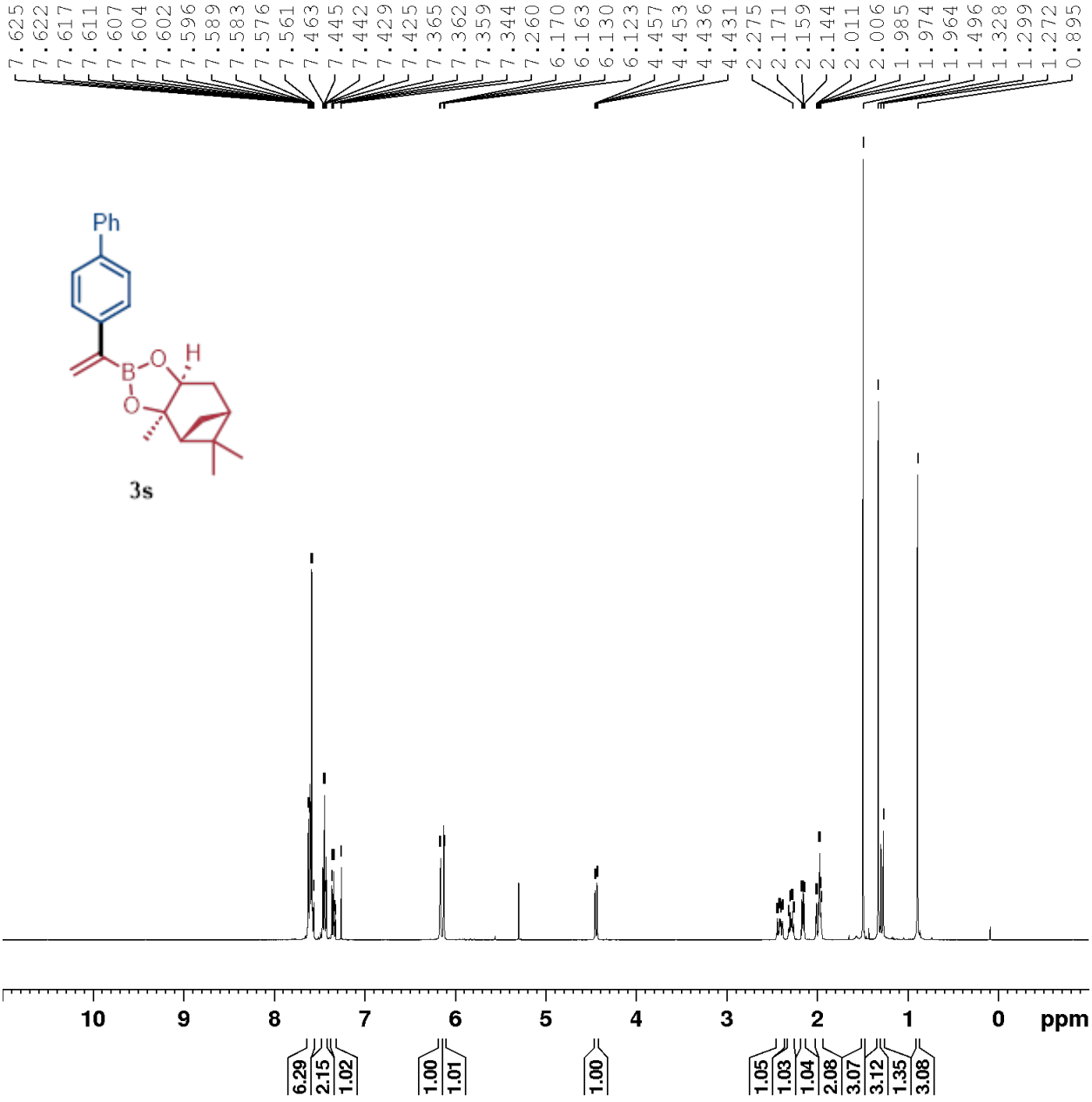
4,4,6-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborinane (3r), ^{13}C, $CDCl_3$, 101 MHz



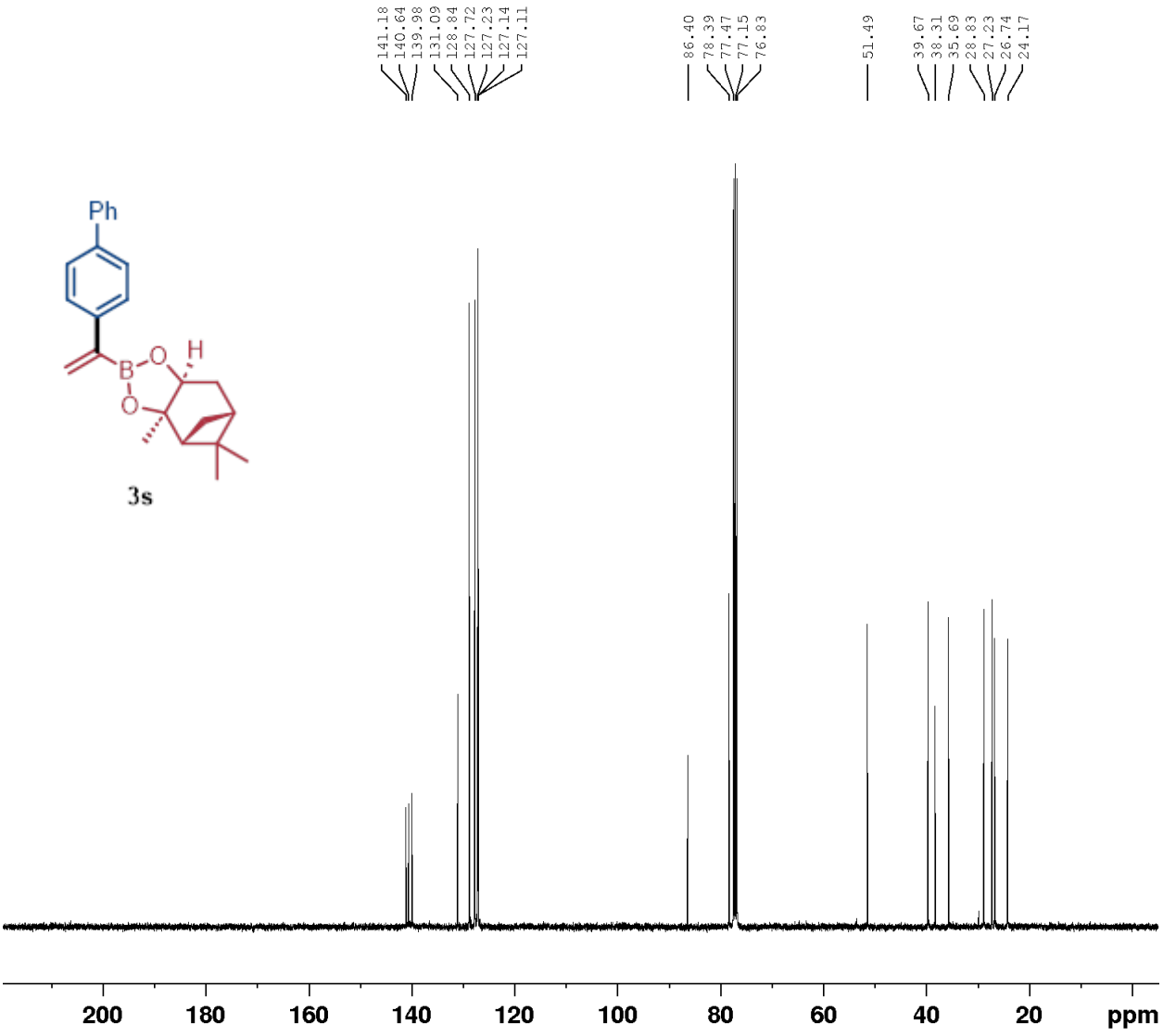
4,4,6-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborinane (3r), ^{11}B, $CDCl_3$, 96 MHz



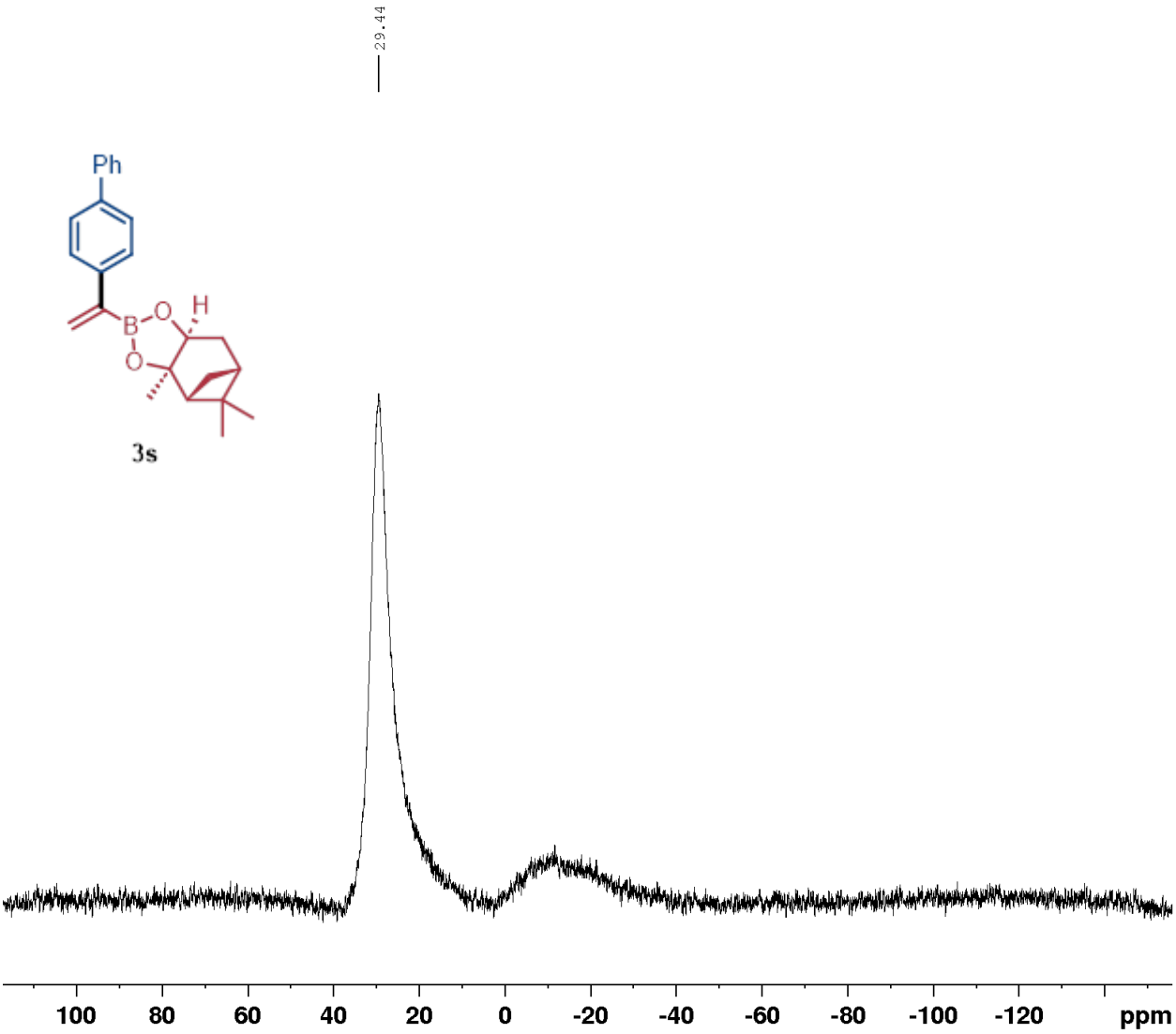
(3aS,7aR)-3a,5,5-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (3s), ^{1}H, $CDCl_3$, 400 MHz



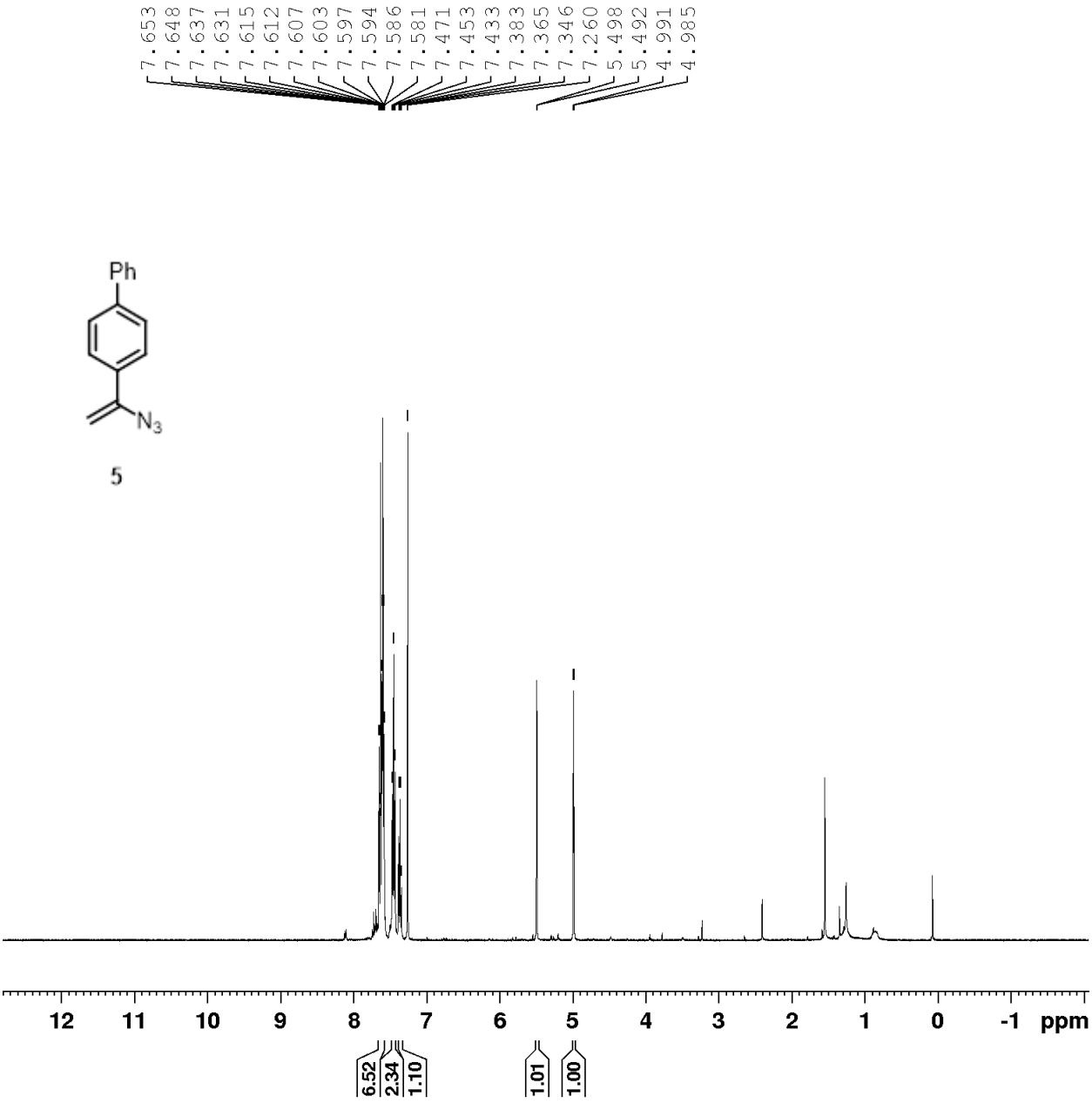
(3aS,7aR)-3a,5,5-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (3s), ^{13}C, $CDCl_3$, 101 MHz



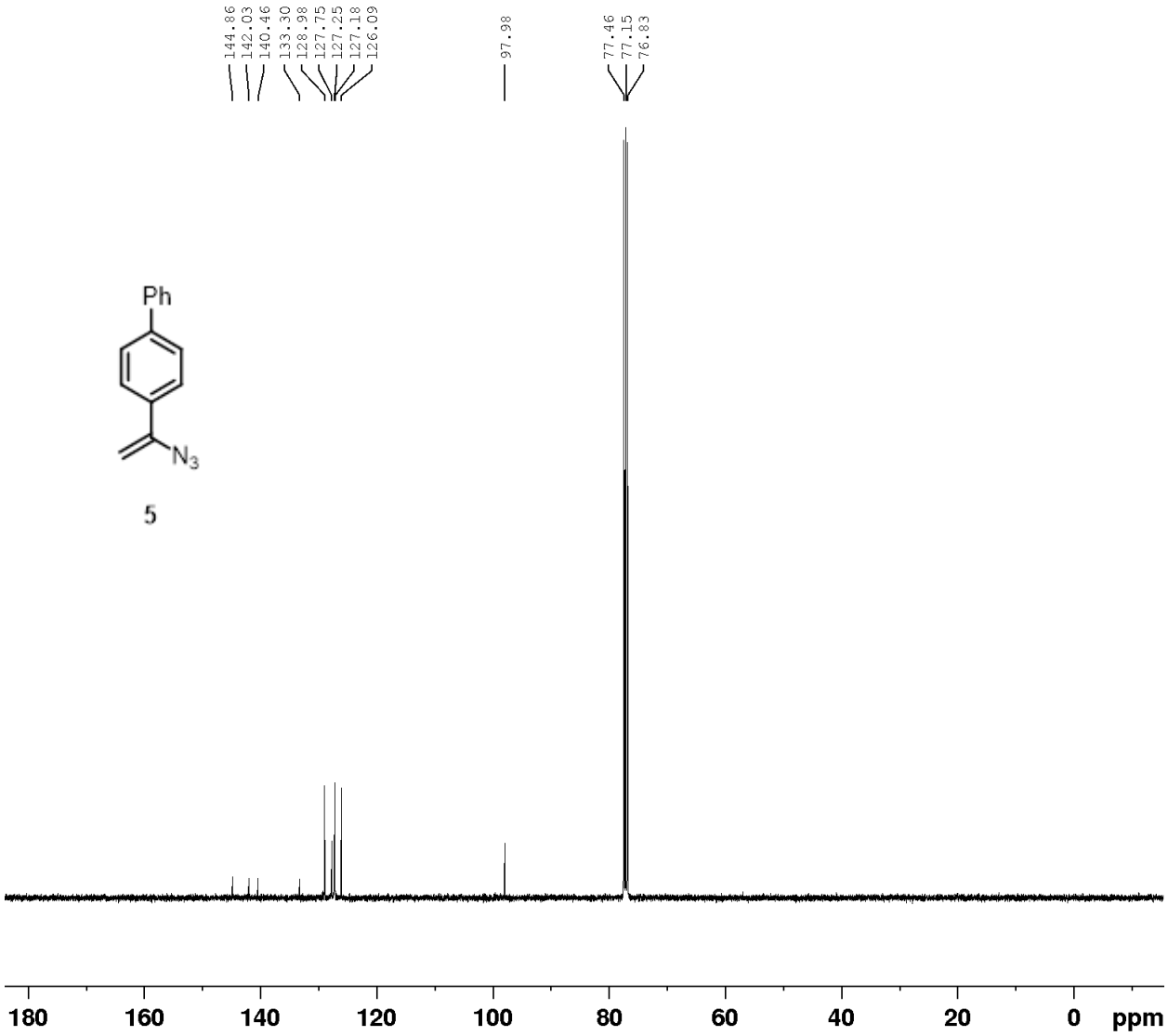
(3aS,7aR)-3a,5,5-trimethyl-2-(1-([1,1'-biphenyl]-4-yl)vinyl)hexahydro-4,6-methanobenzo[d][1,3,2]dioxaborole (3s), ^{11}B, $CDCl_3$, 96 MHz



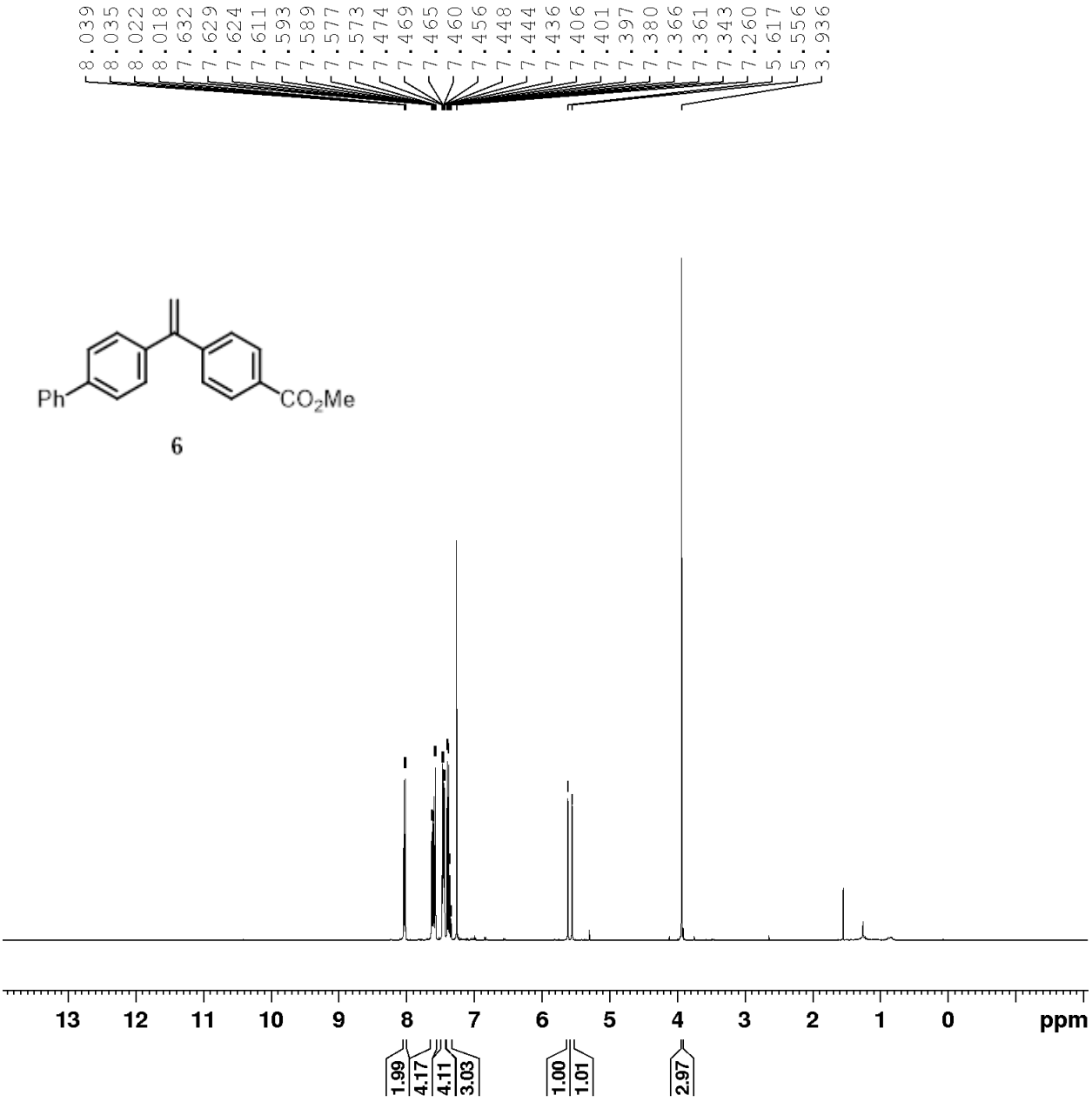
4-(1-azidovinyl)biphenyl (5), ^{1}H, $CDCl_3$, 400 MHz



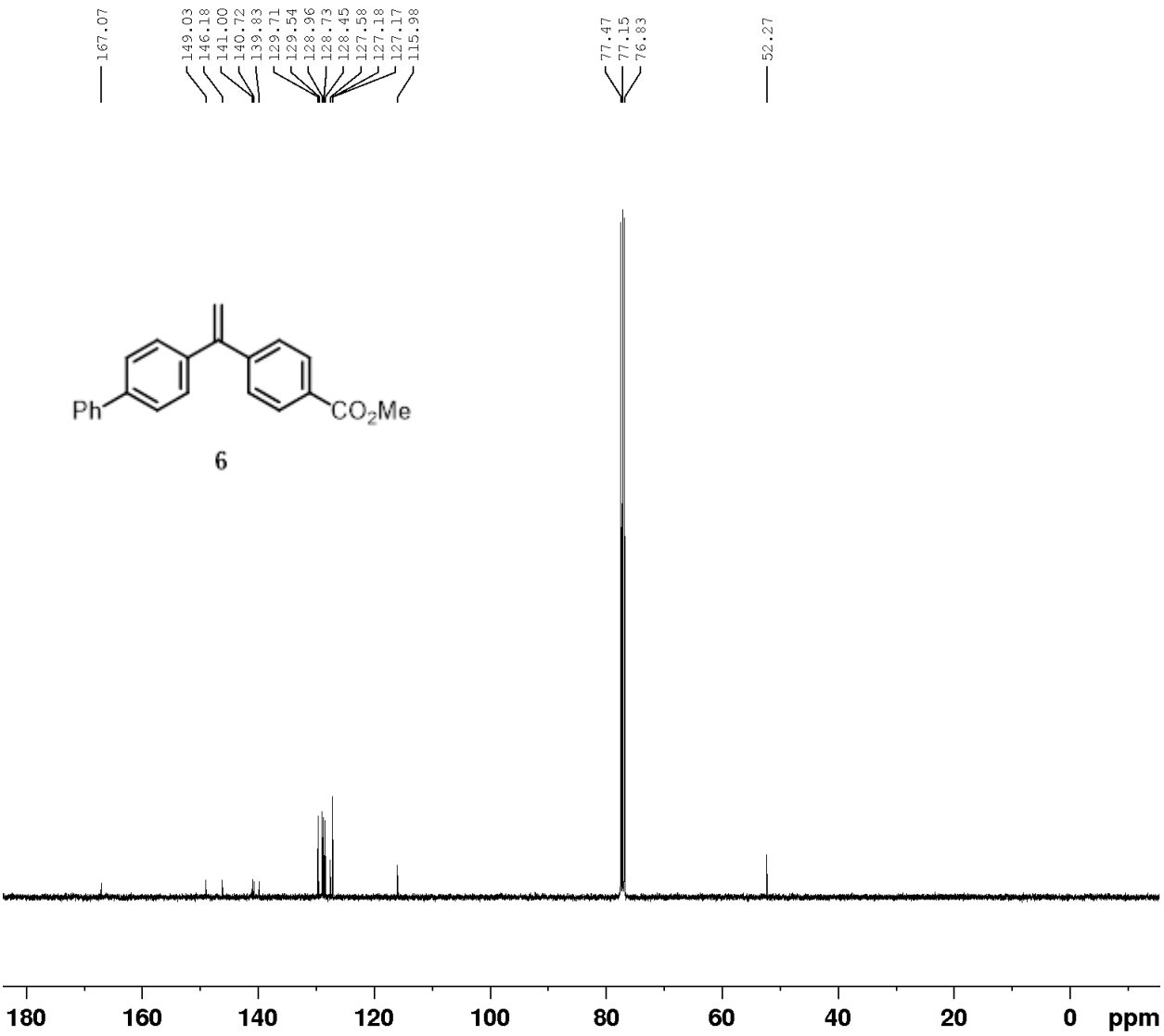
4-(1-azidovinyl)biphenyl (5), ^{13}C, $CDCl_3$, 101 MHz



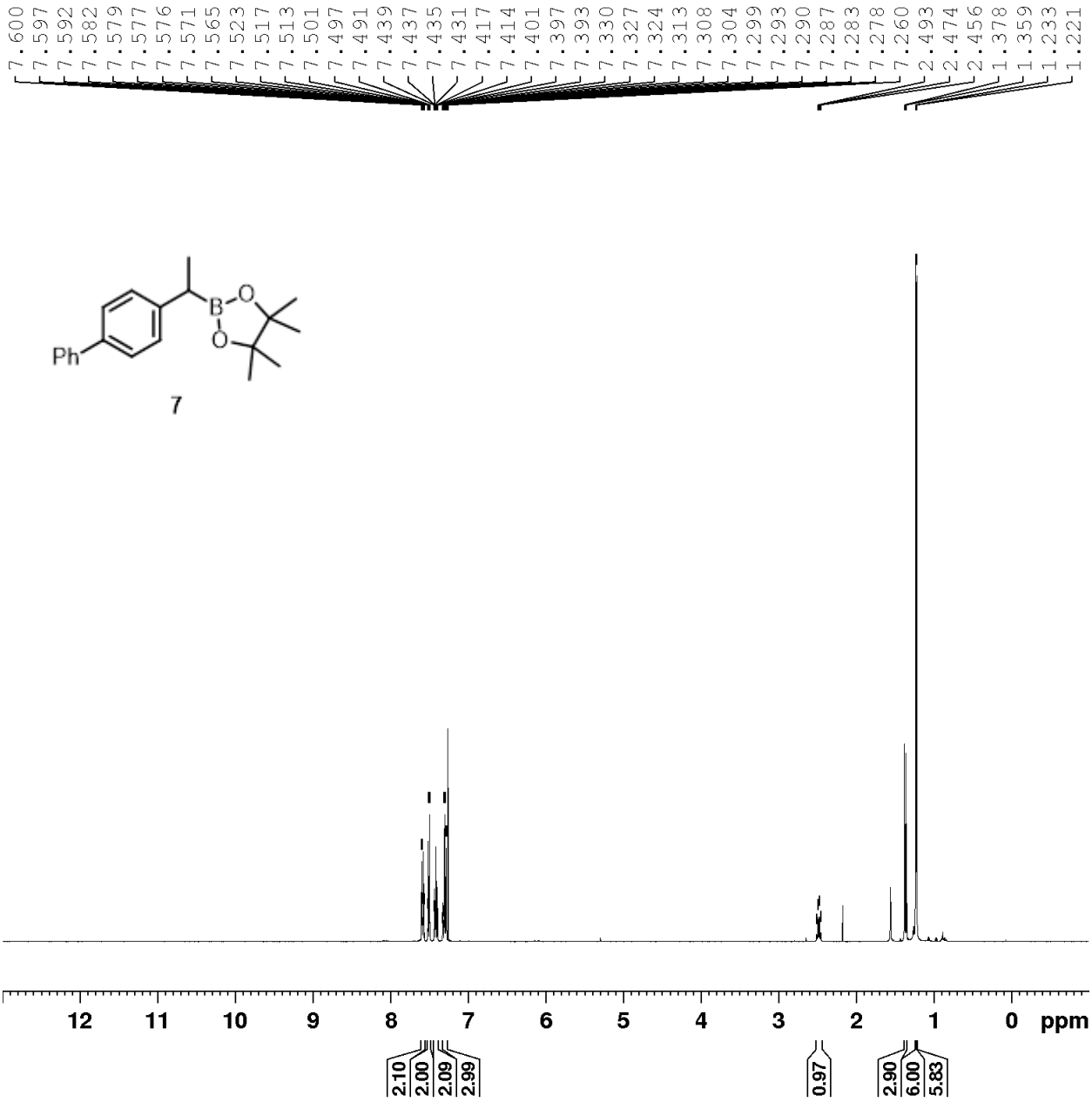
methyl 4-(1-([1,1'-biphenyl]-4-yl)vinyl)benzoate (6), ^{1}H, $CDCl_3$, 400 MHz



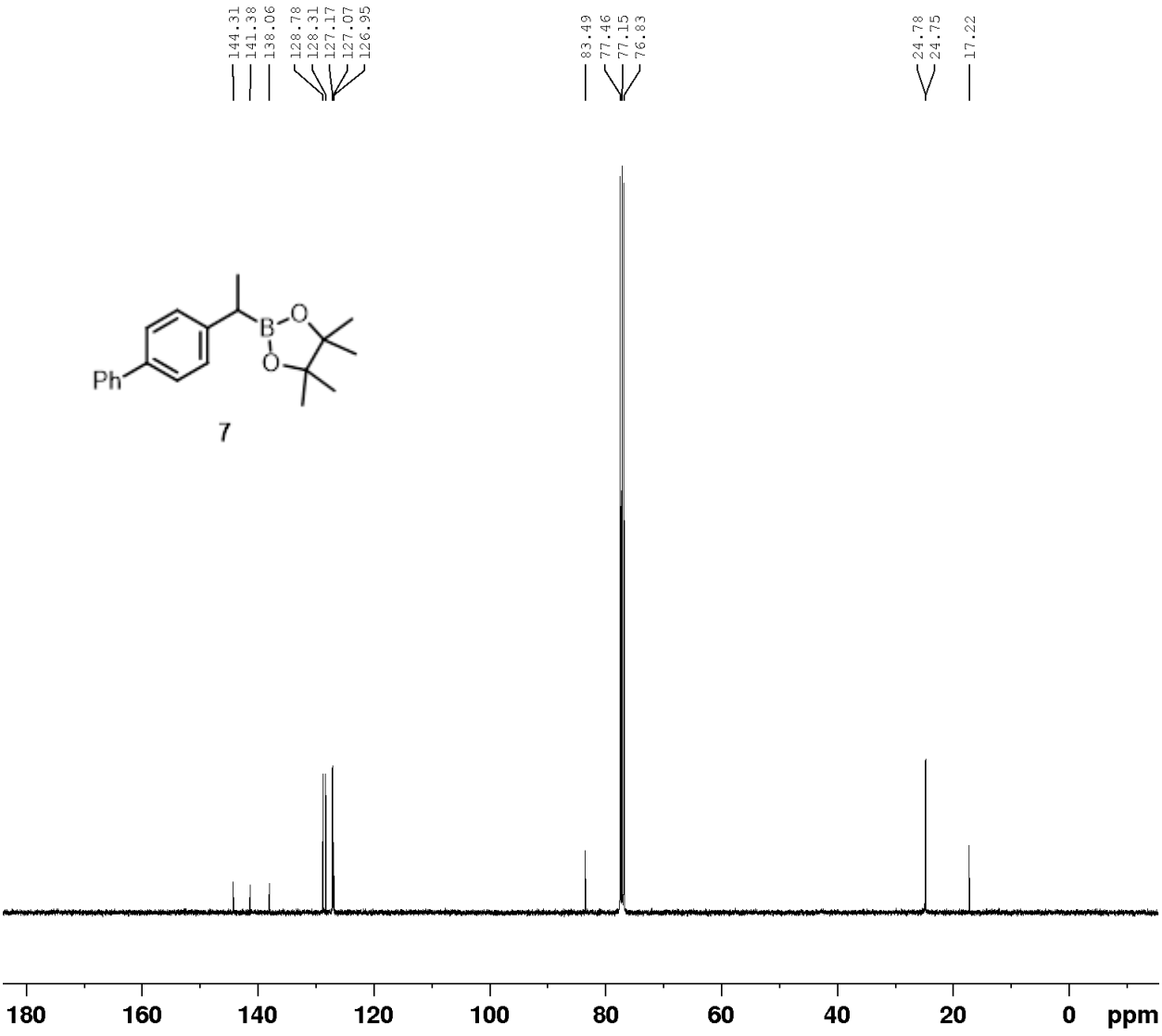
methyl 4-(1-([1,1'-biphenyl]-4-yl)vinyl)benzoate (6), ^{13}C, $CDCl_3$, 101 MHz



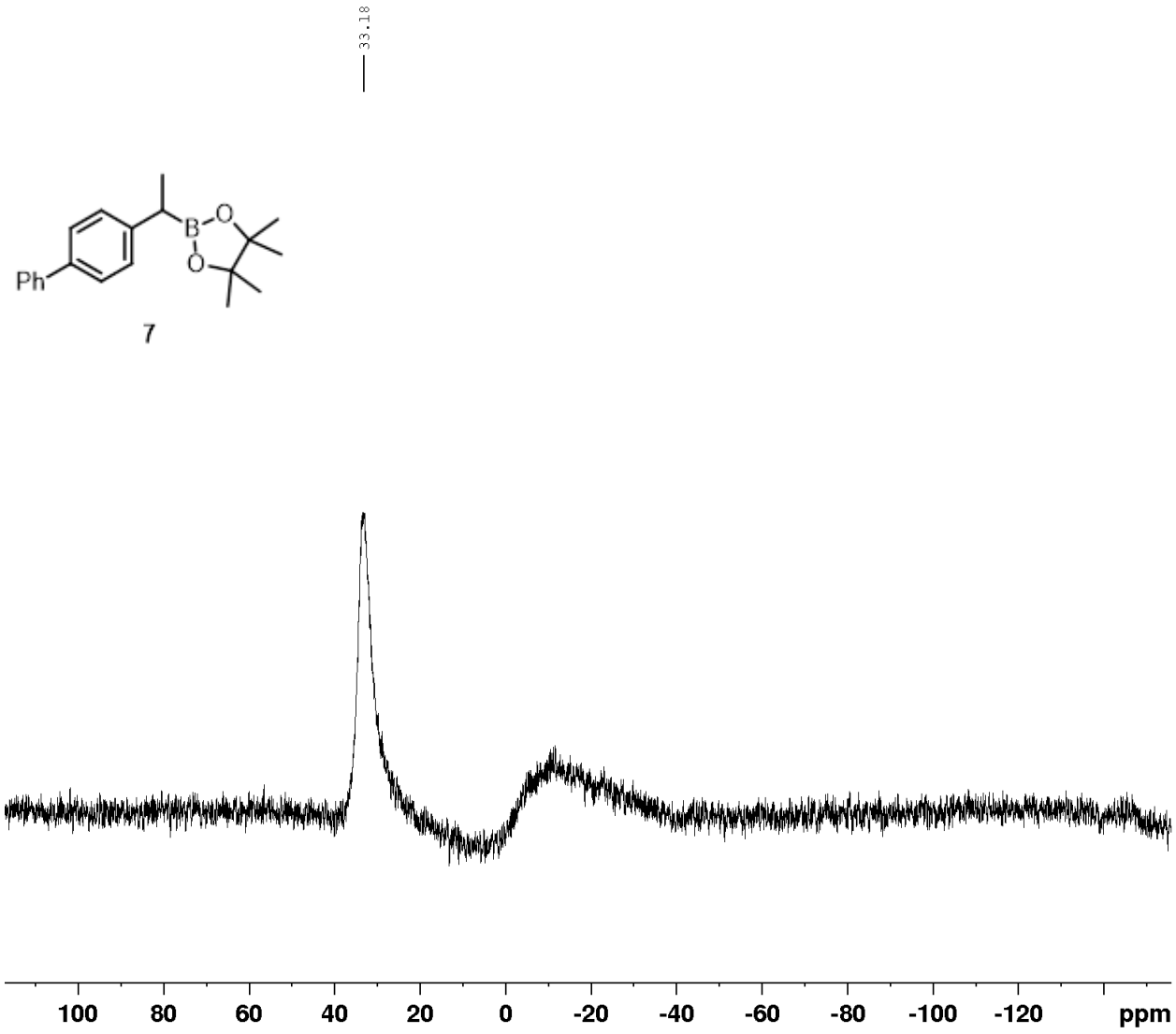
2-(1-([1,1'-biphenyl]-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7), ^{1}H, $CDCl_3$, 400 MHz



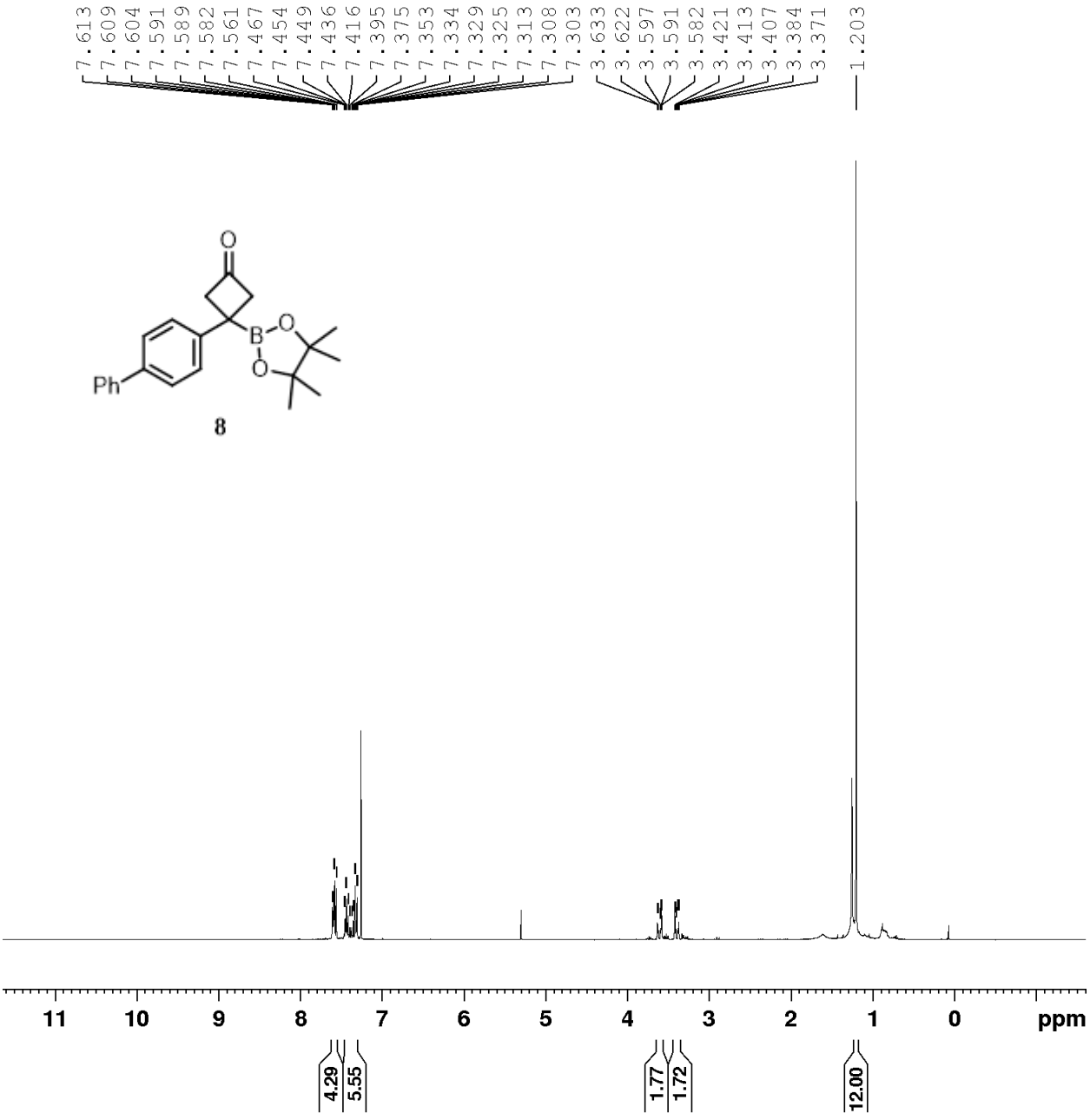
2-(1-([1,1'-biphenyl]-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7), ^{13}C, $CDCl_3$, 101 MHz



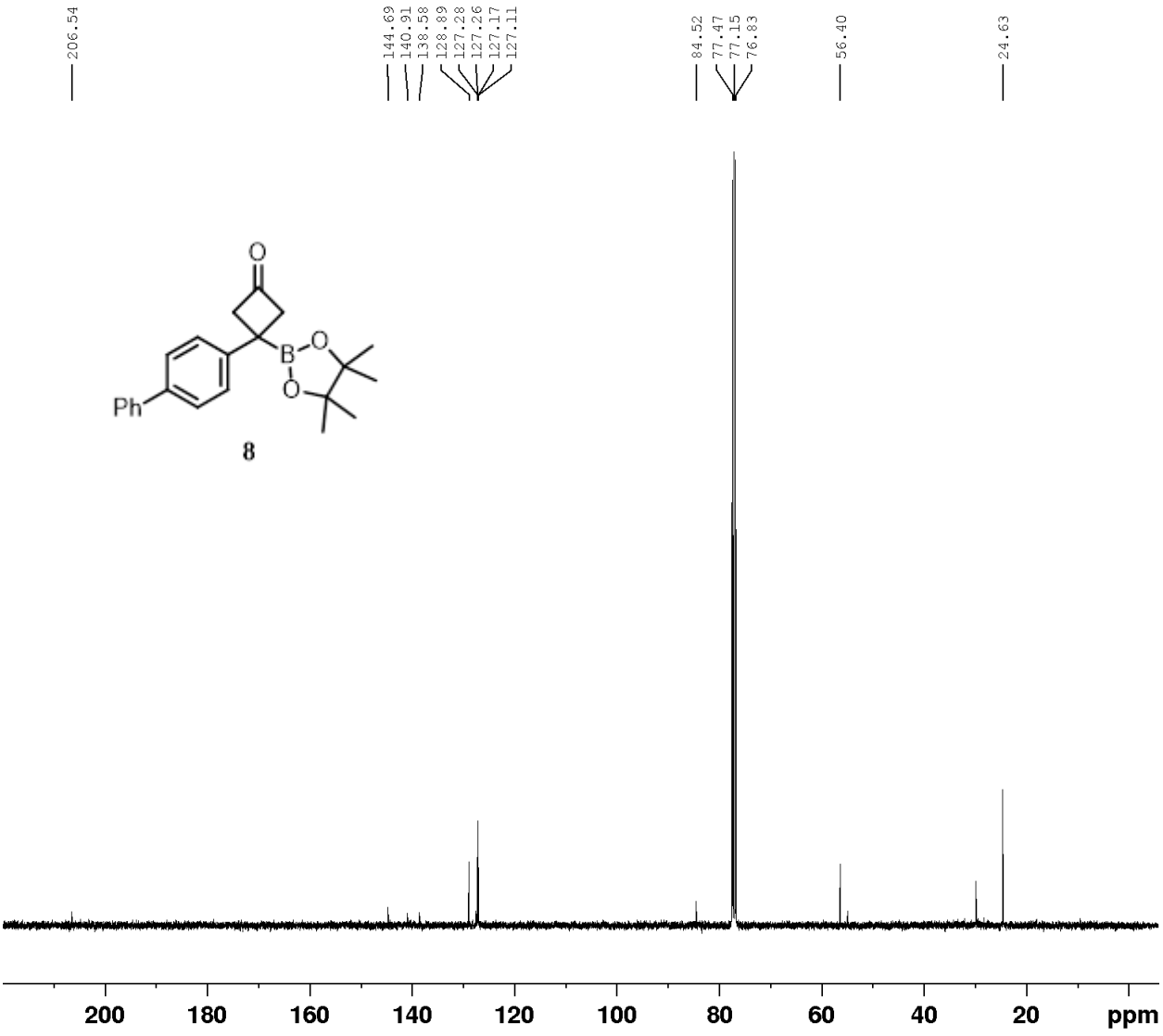
2-(1-([1,1'-biphenyl]-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7), ^{11}B, $CDCl_3$, 96 MHz



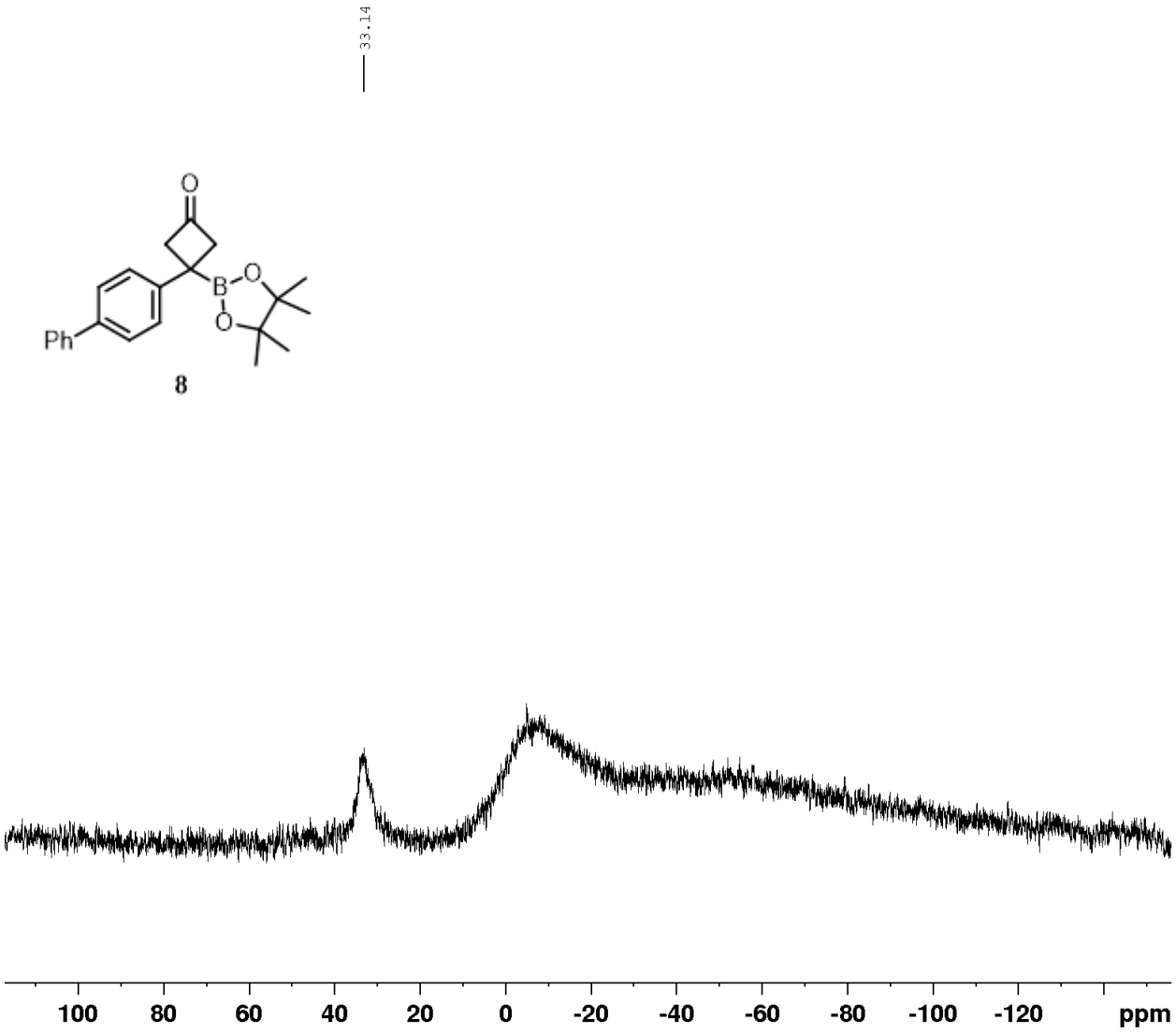
3-([1,1'-biphenyl]-4-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutanone (8), ^{1}H, $CDCl_3$, 400 MHz



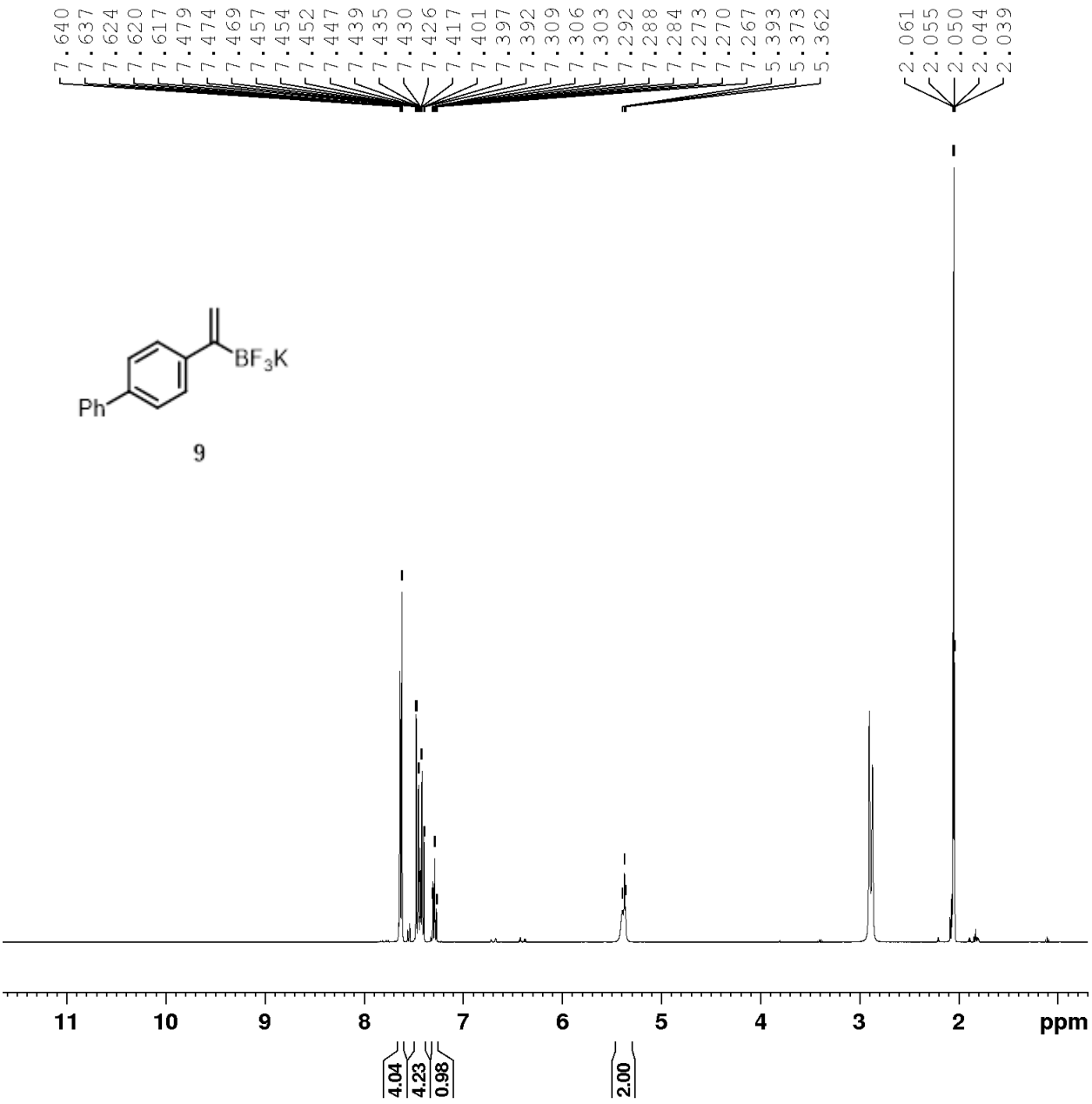
3-([1,1'-biphenyl]-4-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutanone (8), ^{13}C, $CDCl_3$, 101 MHz



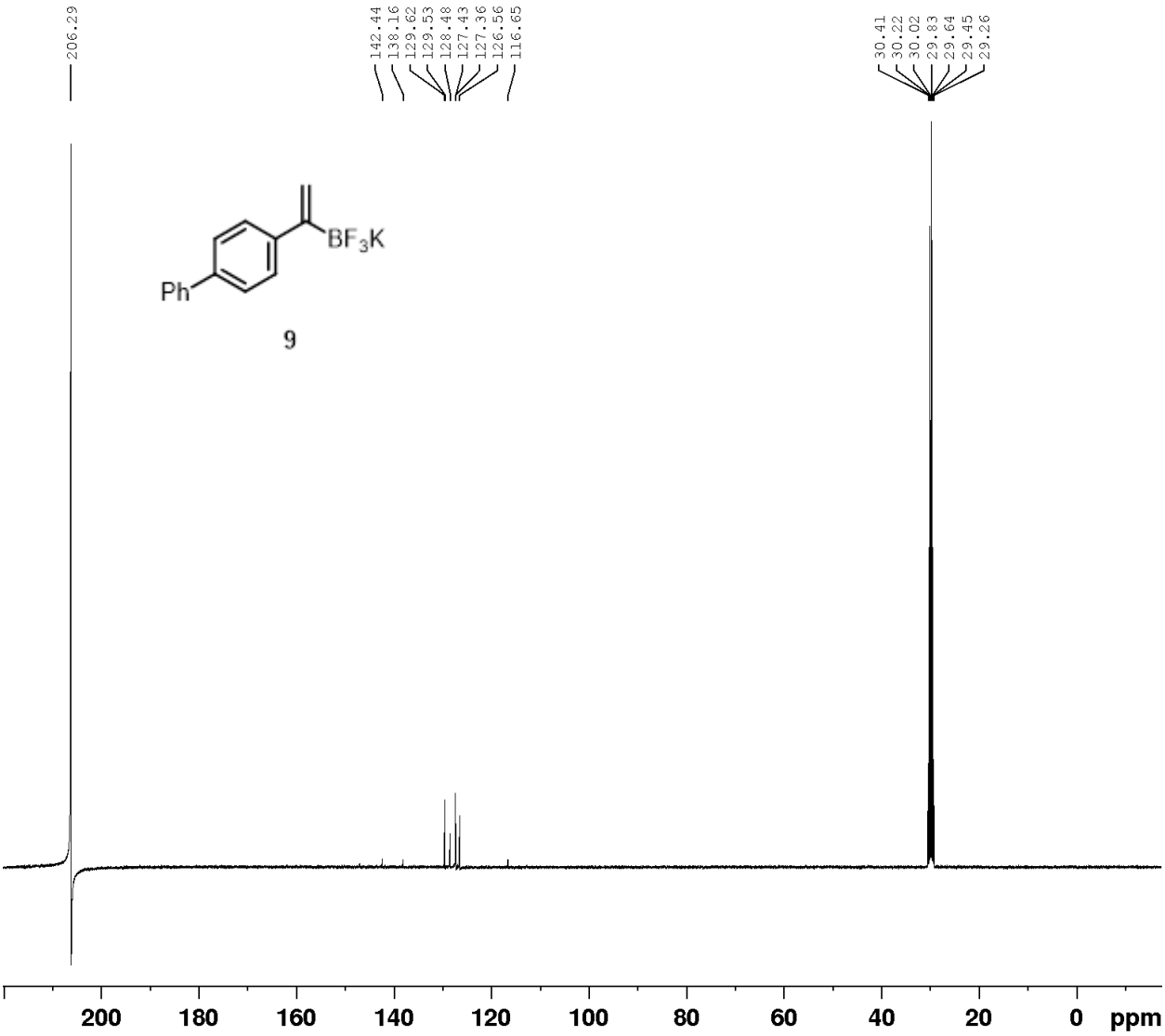
3-([1,1'-biphenyl]-4-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutanone (8), ^{11}B, $CDCl_3$, 96 MHz



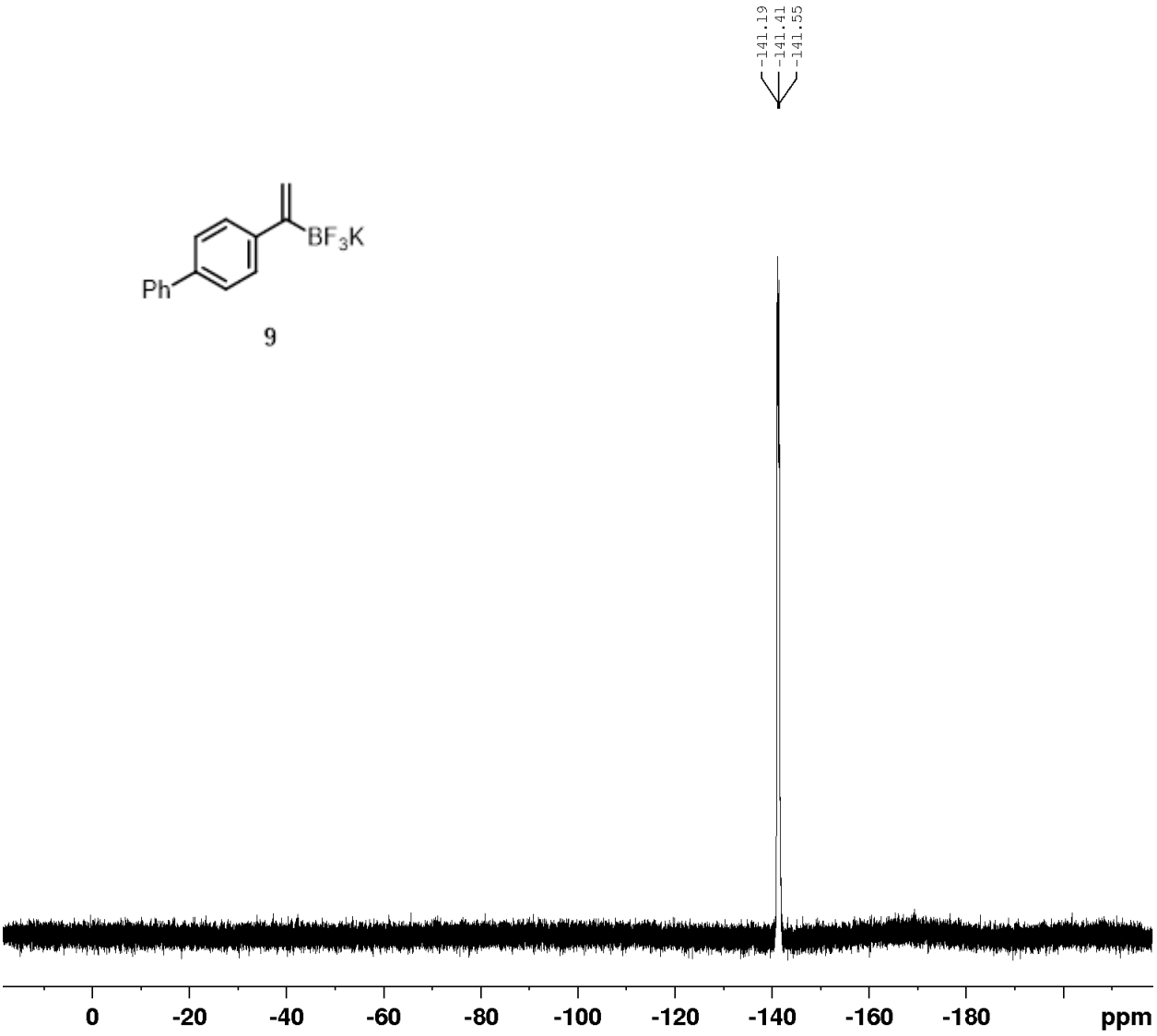
Potassium (1-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate (9) ^{1}H, acetone-*d6*, 400 MHz



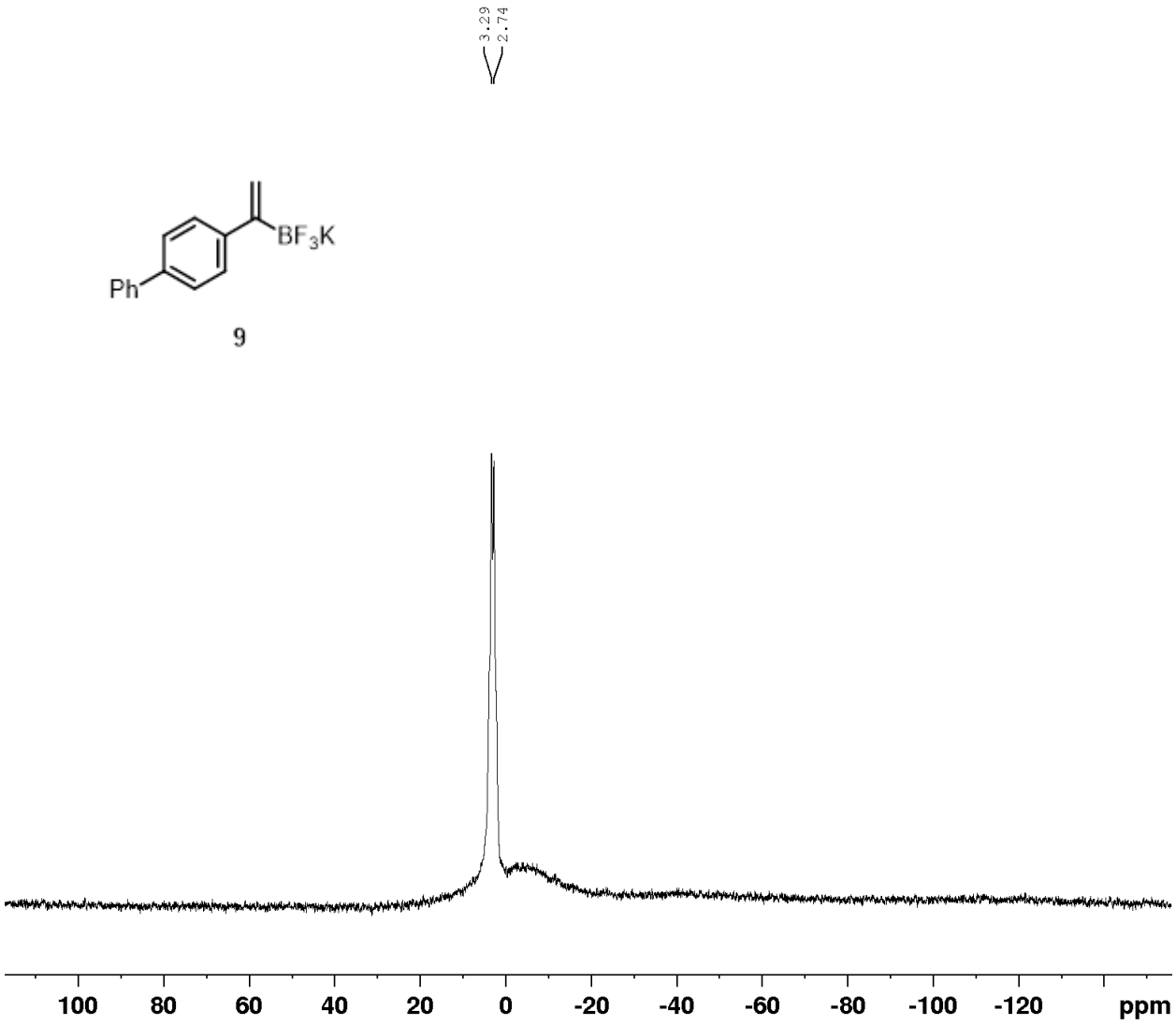
Potassium (1-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate (9) ^{13}C, acetone-*d6*, 101 MHz



Potassium (1-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate (9) ^{19}F, acetone-*d6*, 283 MHz



Potassium (1-([1,1'-biphenyl]-4-yl)vinyl)trifluoroborate (9) ^{11}B, acetone-*d6*, 96 MHz



References

(1) Hartwig, J. F. *Organotransition Metal Chemistry – From Bonding to Catalysis*; University Science Books, 2010.

(2) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. Emergence of Palladium(IV) Chemistry in Synthesis and Catalysis. *Chem. Rev.* **2010**, *110* (2), 824–889.

(3) Fleckenstein, C. A.; Plenio, H. Sterically Demanding Trialkylphosphines for Palladium-Catalyzed Cross Coupling Reactions—Alternatives to P^{t}Bu$_3$. *Chem Soc Rev* **2010**, *39* (2), 694–711.

(4) Echavarren, A. M.; Stille, J. K. Palladium-Catalyzed Coupling of Aryl Triflates with Organostannanes. *J. Am. Chem. Soc.* **1987**, *109* (18), 5478–5486.

(5) Littke, A. F.; Dai, C.; Fu, G. C. Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions. *J. Am. Chem. Soc.* **2000**, *122* (17), 4020–4028.

(6) Proutiere, F.; Schoenebeck, F. Solvent Effect on Palladium-Catalyzed Cross-Coupling Reactions and Implications on the Active Catalytic Species. *Angew. Chem. Int. Ed.* **2011**, *50* (35), 8192–8195.

(7) Keaveney, S. T.; Kundu, G.; Schoenebeck, F. Modular Functionalization of Arenes in a Triply Selective Sequence: Rapid C(sp^2) and C(sp^3) Coupling of C−Br, C−OTf, and C−Cl Bonds Enabled by a Single Palladium(I) Dimer. *Angew. Chem. Int. Ed.* **2018**, *57* (38), 12573–12577.

(8) Miyaura, N. *Cross-Coupling Reaction: A Practical Guide*; Springer, 2002.

(9) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. Novel and Convenient Method for the Stereo- and Regiospecific Synthesis of Conjugated Alkadienes and Alkenynes via the Palladium-Catalyzed Cross-Coupling Reaction of 1-Alkenylboranes with Bromoalkenes and Bromoalkynes. *J. Am. Chem. Soc.* **1985**, *107* (4), 972–980.

(10) Matos, K.; Soderquist, J. A. Alkylboranes in the Suzuki−Miyaura Coupling: Stereochemical and Mechanistic Studies. *J. Org. Chem.* **1998**, *63* (3), 461–470.

(11) Gillie, A.; Stille, J. K. Mechanisms of 1,1-Reductive Elimination from Palladium. *J. Am. Chem. Soc.* **1980**, *102* (15), 4933–4941.

(12) Heck, R. F.; Nolley, J. P. Jr. Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides. *J. Org. Chem.* **1972**, *37* (14), 2320–2322.

(13) Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44* (2), 581–581.

(14) Tamao, K.; Sumitani, K.; Kumada, M. Selective Carbon-Carbon Bond Formation by Cross-Coupling of Grignard Reagents with Organic Halides. Catalysis by Nickel-Phosphine Complexes. *J. Am. Chem. Soc.* **1972**, *94* (12), 4374–4376.

(15) Corriu, R. J. P.; Masse, J. P. Activation of Grignard Reagents by Transition-Metal Complexes. A New and Simple Synthesis of Trans-Stilbenes and Polyphenyls. *J. Chem. Soc. Chem. Commun.* **1972**, No. 3, 144a.

(16) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic

Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes and Bromopyridines. *Tetrahedron Lett.* **1975**, *16* (50), 4467–4470.
(17) Negishi, E.; King, A. O.; Okukado, N. Selective Carbon-Carbon Bond Formation via Transition Metal Catalysis. 3. A Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by the Nickel- or Palladium-Catalyzed Reaction of Aryl- and Benzylzinc Derivatives with Aryl Halides. *J. Org. Chem.* **1977**, *42* (10), 1821–1823.
(18) Kosugi, M.; Shimizu, Y.; Migita, T. Reaction of Allyltin Compounds: II. Facile Preparation of Allyl Ketones via Allyltins. *J. Organomet. Chem.* **1977**, *129* (2), C36–C38.
(19) Milstein, D.; Stille, J. K. A General, Selective, and Facile Method for Ketone Synthesis from Acid Chlorides and Organotin Compounds Catalyzed by Palladium. *J. Am. Chem. Soc.* **1978**, *100* (11), 3636–3638.
(20) Stille, J. K. Palladium Catalyzed Coupling of Organotin Reagents with Organic Electrophiles. **1985**, *57* (12), 1771–1780.
(21) Miyaura, Norio.; Suzuki, Akira. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95* (7), 2457–2483.
(22) Hatanaka, Y.; Hiyama, T. Cross-Coupling of Organosilanes with Organic Halides Mediated by a Palladium Catalyst and Tris(Diethylamino)Sulfonium Difluorotrimethylsilicate. *J. Org. Chem.* **1988**, *53* (4), 918–920.
(23) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angew. Chem. Int. Ed. Engl.* **1995**, *34* (12), 1348–1350.
(24) Louie, J.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides. Mechanistic Studies Lead to Coupling in the Absence of Tin Reagents. *Tetrahedron Lett.* **1995**, *36* (21), 3609–3612.
(25) Surry, D. S.; Buchwald, S. L. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2008**, *47* (34), 6338–6361.
(26) Oestreich, M. *The Mizoroki-Heck Reaction*; Wiley, 2009.
(27) Heck, R. F. Palladium-Catalyzed Reactions of Organic Halides with Olefins. *Acc. Chem. Res.* **1979**, *12* (4), 146–151.
(28) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. α-Regioselectivity in Palladium-Catalyzed Arylation of Acyclic Enol Ethers. *J. Org. Chem.* **1992**, *57* (5), 1481–1486.
(29) Echavarren, A. M.; Stille, J. K. Palladium-Catalyzed Coupling of Aryl Triflates with Organostannanes. *J. Am. Chem. Soc.* **1987**, *109* (18), 5478–5486.
(30) Cabri, W.; Candiani, I. Recent Developments and New Perspectives in the Heck Reaction. *Acc. Chem. Res.* **1995**, *28* (1), 2–7.
(31) Olofsson, K.; Larhed, M.; Hallberg, A. Highly Regioselective Palladium-Catalyzed β-Arylation of N,N-Dialkylallylamines. *J. Org. Chem.* **2000**, *65* (21), 7235–7239.
(32) Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. (Steve). Intermolecular Mizoroki–Heck Reaction of Aliphatic Olefins with High Selectivity for Substitution at the Internal Position. *Angew. Chem. Int. Ed.* **2012**, *51* (24), 5915–5919.
(33) Zou, Y.; Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. (Steve). Selective Arylation and Vinylation at the α Position of Vinylarenes. *Chem. – Eur. J.* **2013**, *19* (10), 3504–3511.
(34) Saa, J. M.; Dopico, M.; Martorell, G.; Garcia-Raso, A. Deoxygenation of Highly Hindered Phenols. *J. Org. Chem.* **1990**, *55* (3), 991–995.

(35) Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. Nickel-Catalyzed Mizoroki–Heck Reaction of Aryl Sulfonates and Chlorides with Electronically Unbiased Terminal Olefins: High Selectivity for Branched Products. *Angew. Chem. Int. Ed.* **2014**, *53* (7), 1858–1861.
(36) G. Märkl, V.; Jin, G. Y.; Schoerner, Ch. 1.5-Diaza-3.7-Diphospha-Cyclooctane. *Tetrahedron Lett.* **1980**, *21* (15), 1409–1412.
(37) Moiseev, D. V.; James, B. R. Phospha-Mannich Reactions of RPH2, R2PH, and R3P. *Phosphorus Sulfur Silicon Relat. Elem.* **2022**, *197* (4), 327–391.
(38) Wiedner, E. S.; Appel, A. M.; Raugei, S.; Shaw, W. J.; Bullock, R. M. Molecular Catalysts with Diphosphine Ligands Containing Pendant Amines. *Chem. Rev.* **2022**, *122* (14), 12427–12474.
(39) Fihri, A.; Luart, D.; Len, C.; Solhy, A.; Chevrin, C.; Polshettiwar, V. Suzuki–Miyaura Cross-Coupling Coupling Reactions with Low Catalyst Loading: A Green and Sustainable Protocol in Pure Water. *Dalton Trans.* **2011**, *40* (13), 3116–3121.
(40) Isbrandt, E. S.; Nasim, A.; Zhao, K.; Newman, S. G. Catalytic Aldehyde and Alcohol Arylation Reactions Facilitated by a 1,5-Diaza-3,7-Diphosphacyclooctane Ligand. *J. Am. Chem. Soc.* **2021**, *143* (36), 14646–14656.
(41) Nasim, A.; Thomas, G. T.; Ovens, J. S.; Newman, S. G. Reductive 1,2-Arylation of Isatins. *Org. Lett.* **2022**, *24* (39), 7232–7236.
(42) Stubbs, J. M.; Chapple, D. E.; Boyle, P. D.; Blacquiere, J. M. Catalyst Pendent-Base Effects on Cyclization of Alkynyl Amines. *ChemCatChem* **2018**, *10* (17), 4001–4009.
(43) Chapple, D. E.; Boyle, P. D.; Blacquiere, J. M. Origin of Stability and Inhibition of Cooperative Alkyne Hydrofunctionalization Catalysts. *ChemCatChem* **2021**, *13* (17), 3789–3800.
(44) Bridge, B. J.; Boyle, P. D.; Blacquiere, J. M. Endo-Selective Iron Catalysts for Intramolecular Alkyne Hydrofunctionalization. *Organometallics* **2020**, *39* (14), 2570–2574.
(45) Isbrandt, E. S.; Chapple, D. E.; Tu, N. T. P.; Dimakos, V.; Beardall, A. M. M.; Boyle, P. D.; Rowley, C. N.; Blacquiere, J. M.; Newman, S. G. Controlling Reactivity and Selectivity in the Mizoroki–Heck Reaction: High Throughput Evaluation of 1,5-Diaza-3,7-Diphosphacyclooctane Ligands. *J. Am. Chem. Soc.* **2024**.
(46) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54* (10), 3451–3479.
(47) Carreras, J.; Caballero, A.; Pérez, P. J. Alkenyl Boronates: Synthesis and Applications. *Chem. – Asian J.* **2019**, *14* (3), 329–343.
(48) West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B. Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **2019**, *119* (24), 12491–12523.
(49) Wu, P.; Givskov, M.; Nielsen, T. E. Reactivity and Synthetic Applications of Multicomponent Petasis Reactions. *Chem. Rev.* **2019**, *119* (20), 11245–11290.
(50) Zweifel, George.; Arzoumanian, Henri.; Whitney, C. C. A Convenient Stereoselective Synthesis of Substituted Alkenes via Hydroboration-Iodination of Alkynes. *J. Am. Chem. Soc.* **1967**, *89* (14), 3652–3653.
(51) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. Catalytic Conjunctive Cross-Coupling Enabled by Metal-Induced Metallate Rearrangement. *Science* **2016**, *351* (6268), 70–74.

(52) Kischkewitz, M.; Okamoto, K.; Mück-Lichtenfeld, C.; Studer, A. Radical-Polar Crossover Reactions of Vinylboron Ate Complexes. *Science* **2017**, *355* (6328), 936–938.
(53) You, C.; Studer, A. Synthesis of 1,3-Bis-(Boryl)Alkanes through Boronic Ester Induced Consecutive Double 1,2-Migration. *Angew. Chem. Int. Ed.* **2020**, *59* (39), 17245–17249.
(54) Silvi, M.; Sandford, C.; Aggarwal, V. K. Merging Photoredox with 1,2-Metallate Rearrangements: The Photochemical Alkylation of Vinyl Boronate Complexes. *J. Am. Chem. Soc.* **2017**, *139* (16), 5736–5739.
(55) Charette, A. B.; Beauchemin, A. Simmons-Smith Cyclopropanation Reaction. In *Organic Reactions*; 2004; pp 1–415. https://doi.org/10.1002/0471264180.or058.01.
(56) Zhao, H.; Lin, Y.; Jiang, M.; Su, B. A General Catalytic Synthetic Strategy for Highly Strained Methylenecyclobutanes and Spiromethylenecyclobutanes. *Chem. Sci.* **2023**, *14* (29), 7897–7904.
(57) Geier, S. J.; Vogels, C. M.; Melanson, J. A.; Westcott, S. A. The Transition Metal-Catalysed Hydroboration Reaction. *Chem. Soc. Rev.* **2022**, *51* (21), 8877–8922.
(58) Hemelaere, R.; Carreaux, F.; Carboni, B. Synthesis of Alkenyl Boronates from Allyl-Substituted Aromatics Using an Olefin Cross-Metathesis Protocol. *J. Org. Chem.* **2013**, *78* (13), 6786–6792.
(59) Coombs, J. R.; Zhang, L.; Morken, J. P. Synthesis of Vinyl Boronates from Aldehydes by a Practical Boron–Wittig Reaction. *Org. Lett.* **2015**, *17* (7), 1708–1711.
(60) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. Palladium-Catalyzed Cross-Coupling Reaction of Bis(Pinacolato)Diboron with 1-Alkenyl Halides or Triflates: Convenient Synthesis of Unsymmetrical 1,3-Dienes via the Borylation-Coupling Sequence. *J. Am. Chem. Soc.* **2002**, *124* (27), 8001–8006.
(61) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. Highly Selective Methods for Synthesis of Internal (α-) Vinylboronates through Efficient NHC–Cu-Catalyzed Hydroboration of Terminal Alkynes. Utility in Chemical Synthesis and Mechanistic Basis for Selectivity. *J. Am. Chem. Soc.* **2011**, *133* (20), 7859–7871.
(62) Yoshida, H.; Takemoto, Y.; Takaki, K. A Masked Diboron in Cu-Catalysed Borylation Reaction: Highly Regioselective Formal Hydroboration of Alkynes for Synthesis of Branched Alkenylborons. *Chem. Commun.* **2014**, *50* (61), 8299–8302.
(63) Chen, J.; Shen, X.; Lu, Z. Cobalt-Catalyzed Markovnikov-Type Selective Hydroboration of Terminal Alkynes. *Angew. Chem. Int. Ed.* **2021**, *60* (2), 690–694.
(64) Gao, Y.; Yazdani, S.; Kendrick IV, A.; Junor, G. P.; Kang, T.; Grotjahn, D. B.; Bertrand, G.; Jazzar, R.; Engle, K. M. Cyclic (Alkyl)(Amino)Carbene Ligands Enable Cu-Catalyzed Markovnikov Protoboration and Protosilylation of Terminal Alkynes: A Versatile Portal to Functionalized Alkenes. *Angew. Chem. Int. Ed.* **2021**, *60* (36), 19871–19878.
(65) Itami, K.; Tonogaki, K.; Ohashi, Y.; Yoshida, J. Rapid Construction of Multisubstituted Olefin Structures Using Vinylboronate Ester Platform Leading to Highly Fluorescent Materials. *Org. Lett.* **2004**, *6* (22), 4093–4096.
(66) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. A Stereoselective Synthesis of 1,6-Diphenyl-1,3,5-Hexatrienes Utilising 4,4,6-Trimethyl-2-Vinyl-1,3,2-Dioxaborinane as a Two-Carbon Alkenyl Building Block. *Org. Biomol. Chem.* **2005**, *3* (17), 3167–3172.
(67) Batsanov, A. S.; Knowles, J. P.; Whiting, A. Mechanistic Studies on the Heck–Mizoroki

Cross-Coupling Reaction of a Hindered Vinylboronate Ester as a Key Approach to Developing a Highly Stereoselective Synthesis of a C1−C7 Z,Z,E-Triene Synthon for Viridenomycin. *J. Org. Chem.* **2007**, *72* (7), 2525–2532.
(68) Liu, Z.; Wei, W.; Xiong, L.; Feng, Q.; Shi, Y.; Wang, N.; Yu, L. Selective and Efficient Synthesis of Trans-Arylvinylboronates and Trans-Hetarylvinylboronates Using Palladium Catalyzed Cross-Coupling. *New J. Chem.* **2017**, *41* (8), 3172–3176.
(69) Molloy, J. J.; Seath, C. P.; West, M. J.; McLaughlin, C.; Fazakerley, N. J.; Kennedy, A. R.; Nelson, D. J.; Watson, A. J. B. Interrogating Pd(II) Anion Metathesis Using a Bifunctional Chemical Probe: A Transmetalation Switch. *J. Am. Chem. Soc.* **2018**, *140* (1), 126–130.
(70) Jutand, A.; Mosleh, A. Rate and Mechanism of Oxidative Addition of Aryl Triflates to Zerovalent Palladium Complexes. Evidence for the Formation of Cationic (σ-Aryl)Palladium Complexes. *Organometallics* **1995**, *14* (4), 1810–1817.
(71) Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. An Improved Palladium-Catalyzed Conversion of Aryl and Vinyl Triflates to Bromides and Chlorides. *Org. Lett.* **2011**, *13* (18), 4974–4976.
(72) Huang, L.; Ackerman, L. K. G.; Kang, K.; Parsons, A. M.; Weix, D. J. LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates. *J. Am. Chem. Soc.* **2019**, *141* (28), 10978–10983.
(73) Reid, W. B.; Spillane, J. J.; Krause, S. B.; Watson, D. A. Direct Synthesis of Alkenyl Boronic Esters from Unfunctionalized Alkenes: A Boryl-Heck Reaction. *J. Am. Chem. Soc.* **2016**, *138* (17), 5539–5542.
(74) Becica, J.; Glaze, O. D.; Hruszkewycz, D. P.; Dobereiner, G. E.; Leitch, D. C. The Influence of Additives on Orthogonal Reaction Pathways in the Mizoroki–Heck Arylation of Vinyl Ethers. *React. Chem. Eng.* **2021**, *6* (7), 1212–1219.
(75) Reeves, E. K.; Bauman, O. R.; Mitchem, G. B.; Neufeldt, S. R. Solvent Effects on the Selectivity of Palladium-Catalyzed Suzuki-Miyaura Couplings. *Isr. J. Chem.* **2020**, *60* (3–4), 406–409.
(76) Molander, G. A.; Brown, A. R. Suzuki−Miyaura Cross-Coupling Reactions of Potassium Vinyltrifluoroborate with Aryl and Heteroaryl Electrophiles. *J. Org. Chem.* **2006**, *71* (26), 9681–9686.
(77) Molander, G. A.; Ellis, N. Organotrifluoroborates: Protected Boronic Acids That Expand the Versatility of the Suzuki Coupling Reaction. *Acc. Chem. Res.* **2007**, *40* (4), 275–286.
(78) Jonet, A.; Dassonville-Klimpt, A.; Da Nascimento, S.; Leger, J.-M.; Guillon, J.; Sonnet, P. First Enantioselective Synthesis of 4-Aminoalcohol Quinoline Derivatives through a Regioselective SN2 Epoxide Opening Mechanism. *Tetrahedron Asymmetry* **2011**, *22* (2), 138–148.
(79) Jayaram, V.; Sridhar, T.; Sharma, G. V. M.; Berrée, F.; Carboni, B. Synthesis of Polysubstituted Isoquinolines and Related Fused Pyridines from Alkenyl Boronic Esters via a Copper-Catalyzed Azidation/Aza-Wittig Condensation Sequence. *J. Org. Chem.* **2018**, *83* (2), 843–853.
(80) Prysiazhniuk, K.; Polishchuk, O.; Shulha, S.; Gudzikevych, K.; Datsenko, O. P.; Kubyshkin, V.; Mykhailiuk, P. K. Borylated Cyclobutanes via Thermal [2 + 2]-Cycloaddition. *Chem. Sci.* **2024**.
(81) Wang, Z.-Y.; Ma, B.; Xu, H.; Wang, X.; Zhang, X.; Dai, H.-X. Arylketones as Aryl Donors in

Palladium-Catalyzed Suzuki–Miyaura Couplings. *Org. Lett.* **2021**, *23* (21), 8291–8295.
(82) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A. Synthesis and Structure-Activity Relationships of Novel Retinoid X Receptor-Selective Retinoids. *J. Med. Chem.* **1994**, *37* (18), 2930–2941.
(83) Gniadecki, R.; Assaf, C.; Bagot, M.; Dummer, R.; Duvic, M.; Knobler, R.; Ranki, A.; Schwandt, P.; Whittaker, S. The Optimal Use of Bexarotene in Cutaneous T-cell Lymphoma. *Br. J. Dermatol.* **2007**, *157* (3), 433–440.
(84) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and Preparation of New Palladium Precatalysts for C–C and C–N Cross-Coupling Reactions. *Chem. Sci.* **2013**, *4* (3), 916–920.
(85) Hitosugi, S.; Tanimoto, D.; Nakanishi, W.; Isobe, H. A Facile Chromatographic Method for Purification of Pinacol Boronic Esters. *Chem. Lett.* **2012**, *41* (9), 972–973.
(86) Oka, N.; Yamada, T.; Sajiki, H.; Akai, S.; Ikawa, T. Aryl Boronic Esters Are Stable on Silica Gel and Reactive under Suzuki–Miyaura Coupling Conditions. *Org. Lett.* **2022**, *24* (19), 3510–3514.
(87) Ho, T. D.; Lee, B. J.; Tan, C.; Utley, J. A.; Ngo, N. Q.; Hull, K. L. Efficient Synthesis of α-Haloboronic Esters via Cu-Catalyzed Atom Transfer Radical Addition. *J. Am. Chem. Soc.* **2023**, *145* (50), 27230–27235.
(88) Goossen, L. J.; Rodríguez, N.; Linder, C. Decarboxylative Biaryl Synthesis from Aromatic Carboxylates and Aryl Triflates. *J. Am. Chem. Soc.* **2008**, *130* (46), 15248–15249.
(89) Ping, Y.; Wang, R.; Wang, Q.; Chang, T.; Huo, J.; Lei, M.; Wang, J. Synthesis of Alkenylboronates from N-Tosylhydrazones through Palladium-Catalyzed Carbene Migratory Insertion. *J. Am. Chem. Soc.* **2021**, *143* (26), 9769–9780.
(90) Fordham, J. M.; Grayson, M. N.; Aggarwal, V. K. Vinylidene Homologation of Boronic Esters and Its Application to the Synthesis of the Proposed Structure of Machillene. *Angew. Chem. Int. Ed.* **2019**, *58* (43), 15268–15272.
(91) Wu, S.-W.; Liu, F. Synthesis of α-Fluoroketones from Vinyl Azides and Mechanism Interrogation. *Org. Lett.* **2016**, *18* (15), 3642–3645.
(92) Yang, C.; Gao, Y.; Bai, S.; Jiang, C.; Qi, X. Chemoselective Cross-Coupling of Gem-Borazirconocene Alkanes with Aryl Halides. *J. Am. Chem. Soc.* **2020**, *142* (26), 11506–11513.